

Tânia Filipa Sobrinho dos Santos

OPTIMIZING PROCEDURES IN STEREOTACTIC RADIOSURGERY

Dissertation presented to the Physics Department at
University of Coimbra to obtain the
Master's degree in Biomedical Engineering

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Tânia Filipa Sobrinho dos Santos

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obtain the Master's degree in Biomedical Engineering*

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IPOCFG, E.P.E.



IPOC - FG, EPE

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“Para ser grande sê inteiro: nada
Teu exagera ou exclui.
Sê todo em cada coisa. Põe quanto és
No mínimo que fazes.
Assim em cada lago a lua toda
Brilha, porque alta vive.”

Ricardo Reis

Abstract

The present phase of stereotactic radiosurgery treatments started at IPOCFG in 2008, after a modernization of the radiotherapy department. Till now, around 400 brain lesions were treated, the majority of which were brain metastases.

Radiosurgery is a treatment modality where high doses of ionizing radiation are delivered in a single fraction with high accuracy to a small and well-defined intracranial target while minimizing the irradiation of the surrounding normal brain tissue.

At IPOCFG, radiosurgery is performed using a linear accelerator equipped with a micro-multileaf collimator of Brainlab (m3 mMLC) and a dynamic conformal arc irradiation technique using 6 to 7 noncoplanar arcs centred at the isocenter which is located at the centre of mass of the lesion.

The treatment procedure is completed in a single day, over a set of steps, carried out by a multidisciplinary team. My master's project focused on the treatment planning phase. The purposes were: 1) to configure the treatment parameters according to the tumour type and location in order to create plan templates that speed up and optimize the planning process; and 2) from the casuistic of the lesions treated at IPOCFG to evaluate if the acquisition of a 160 MLC with 5 mm leaf width at isocenter (MLC-160) would enable to dispense the use of the m3 mMLC without significantly compromising the quality of the clinical treatment plans.

During treatment planning, the quality of a radiosurgery treatment plan is assessed through dose-volume indices that score the dose distribution in terms of coverage and conformity. To understand the treatment plan quality evaluation, a review and critical analysis of the dose-volume indices described in the literature was made, as a starting point of this project.

Subsequently, specific templates for acoustic neurinoma and different metastatic lesions were established and evaluated in terms of plan quality. Applying the proposed specific templates the compliance to local plan acceptance quality criteria was achieved with adjustment of the mMLC shape for just two/three arcs used for treatment. This allowed a considerable reduction – to around 1/3 to 1/2 of the treatment planning time.

Moreover, the casuistic of brain metastases treated at IPOCFG was reported and the outcome evaluated for 250 metastases in 168 patients treated between March 2008 and December 2014. Median overall survival was 9 months from the date of the

treatment. Patient's age and primary tumour location were identified as significant predictive factors for survival. Local control was achieved in 85.2% of the evaluated brain metastases and no significant factors were associated with the local tumour progression.

Finally, the loss in terms of plan quality if the m3 mMLC was replaced on the linear accelerator by the MLC-160 was studied and it was demonstrated that the replacement would not represent a beneficial option. The main drawbacks would be less effective conformity and organ at risk sparing, mainly for irregular lesions and lesions located at close proximity of critical structures.

Keywords: Stereotactic radiosurgery, treatment planning, plan quality, dose-volume indices, multileaf collimator, leaf width

Resumo

A atual fase de tratamentos de radiocirurgia estereotáxica começou no IPOCFG em 2008, depois da modernização do serviço de radioterapia. Até ao momento, já foram tratadas mais de 400 lesões cerebrais, sendo a maioria metástases.

A radiocirurgia estereotáxica é uma modalidade terapêutica em que altas doses de radiação ionizante são administradas numa única fração, a lesões intracranianas de pequenas dimensões e com limites bem definidos. Desta forma consegue-se atingir o volume a tratar, poupando os tecidos cerebrais são envolventes.

No IPOCFG, a radiocirurgia é realizada usando um micro-colimador multifolhas da Brainlab (m3 mMLC), com completa integração num acelerador linear, em modo de fotões de 6 MV. A técnica de irradiação baseia-se na distribuição de dose por 6 a 7 arcos não coplanares convergentes no centro de massa da lesão (isocentro).

Este tratamento é feito num único dia, integrando um conjunto de passos, levados a cabo por uma equipa multidisciplinar. O meu projeto de mestrado centrou-se na fase de planeamento do tratamento. Os objetivos foram: 1) configurar os parâmetros de tratamento de acordo com o tipo de tumor e a sua localização, no sentido de constituir planos-modelo para agilizar e otimizar o processo de planeamento; e 2) face à casuística de lesões tratadas no IPOCFG avaliar se a aquisição de um MLC de 160 folhas com 5 mm de largura (MLC-160) permitiria dispensar o uso do m3 mMLC sem comprometer significativamente a qualidade dos planos clínicos.

Durante a fase de planeamento do tratamento, a qualidade da distribuição de dose avalia-se através índices de dose-volume. Estes índices são uma ferramenta muito poderosa que facilita a tomada de decisões durante a comparação dosimétrica de vários planos. Por isso, começou por ser feita uma revisão bibliográfica e uma análise crítica dos índices de qualidade descritos na literatura.

Subsequentemente, foram desenvolvidos planos-modelo específicos para o tratamento de casos clínicos de neurinoma do acústico e metástases cerebrais e avaliada a qualidade dos planos. A aplicação destes modelos e o ajuste da forma das folhas do m3 em 2 ou 3 arcos dos 6 a 7 usados no tratamento permitiu uma redução do tempo de planeamento em cerca de 1/2 - 1/3.

Adicionalmente, foi feita uma análise da casuística de lesões metastáticas tratadas no IPOCFG, e avaliado o resultado do tratamento em termos de sobrevivência e controlo tumoral local. Entre Março de 2008 e Dezembro de 2014, foram tratados 168

doentes com um total de 250 metástases cerebrais. O tempo de sobrevida mediano estimado foi de 9 meses após a data de tratamento. A idade do doente e a localização do tumor primário foram identificados como fatores que afetam a sobrevivência. Quanto ao controlo local, 85.2% das metástases cerebrais avaliadas foram controladas ou desapareceram, sendo que não foram encontrados fatores associados com a progressão local do tumor.

Por último, foi estudado em que medida é que a eventual substituição do m3 pelo MLC-160, contribuiria ou não para a degradação da qualidade dos planos de tratamento. Foi demonstrado que a dispensa do m3 não representa uma boa opção. Os principais problemas associados a essa mudança residiriam na diminuição da conformidade da distribuição dose, bem como numa proteção menos efetiva das estruturas críticas, principalmente quando se consideram lesões irregulares ou próximas de órgãos de risco.

Palavras-chave: Radiocirurgia estereotáxica, planeamento do tratamento, qualidade dos planos, índices dose-volume, colimador multifolhas, largura das folhas

Contents

Agradecimientos	i
Abstract.....	v
Resumo	vii
Contents	ix
List of Figures	xiii
List of Tables	xv
1 Introduction.....	1
1.1 Radiosurgery at IPOCFG, E.P.E.....	3
1.2 Motivation and Goals.....	4
1.3 Organization of the Dissertation	5
2 Dose-volume Quality Indices for Radiosurgery Treatment Plan Assessment: A Review	7
Abstract.....	9
2.1 Introduction	9
2.1.1 Evolution of Radiosurgery.....	10
2.1.2 Radiosurgery Treatment Assessment.....	11
2.2 Dose-volume quality indices: definitions and discussion	11
2.2.1 Coverage Indices.....	11
2.2.2 Homogeneity Indices	12
2.2.3 Conformity Indices	13
2.3 Conclusion	21
2.4 References	23
3 Definition and evaluation of a template to speed up radiosurgery treatment planning of acoustic neurinomas	25
Abstract.....	27
3.1 Introduction.....	28
3.2 Methods and Materials	29
3.2.1 Target Lesions.....	29
3.2.2 Organ at Risk	30
3.2.3 Treatment Technique	30
3.2.4 Treatment planning	31
3.2.5 Treatment plan Evaluation.....	35
3.2.6 Specific Template Creation	36
3.3 Results and Discussion.....	37

3.4 Conclusions	43
3.5 Appendix: COIN' vs COSI for pituitary adenomas	44
3.6 References	47
4 Stereotactic Radiosurgery for the treatment of brain metastases: definition and evaluation of templates to speed up treatment planning	49
Abstract	51
4.1 Introduction	52
4.2 Methods and Materials	52
4.2.1 Target Lesions	52
4.2.2 Treatment technique and treatment planning	53
4.2.3 Brain mapping	53
4.2.4 Specific template creation	55
4.2.5 Treatment plan evaluation	56
4.3 Results and Discussion	57
4.4 Conclusions	62
4.5 References	63
5 Stereotactic Radiosurgery of Brain Metastases: Analysis of Outcome	65
Abstract	67
5.1 Introduction	68
5.2 Methods and Materials	69
5.2.1 Lesion characteristics and SRS procedures	69
5.2.2 Follow-up and outcomes analysis	71
5.2.3 Statistical analysis	72
5.3 Results	72
5.3.1 Overall Survival	72
5.3.2 Local Control	75
5.4 Discussion	75
5.5 Conclusion	77
5.6 References	79
6 Dosimetric comparison of multileaf collimator systems for intracranial stereotactic radiosurgery	83
Abstract	85
6.1 Introduction	86
6.2 Methods and Materials	87
6.2.1 Patients selection	87
6.2.2 Collimators	88
6.2.3 Machine Profiles Comparison	89

6.2.4 Treatment planning	90
6.2.5 Plan quality evaluation parameters	91
6.2.6 Statistical Analysis.....	92
6.3 Results	92
6.3.1 PTV coverage, Dose conformity and Conformity/ Gradient index	92
6.3.2 Minimum and Maximum target doses	94
6.3.3 Dose to critical structures	94
6.3.4 Dose to normal tissue.....	96
6.4 Discussion	97
6.5 Conclusions	99
6.6 References	100
7 Conclusions	101

List of Figures

Figure 1.1 – The basic steps of a SRS treatment at IPOCFG.	4
Figure 2.1 – Definition of the volumes used in dose-volume quality indices. The solid line shows the target volume, V_T ; the dotted line shows the prescription isodose, pi ; represented in grey is the volume within the target receiving at least the prescription isodose, $V_{T,pi}$	12
Figure 2.2 – COSI vs CI for three different plans and one critical organ. Each plan is a point in the plane. The Perfect plan scores at $COSI=CI=1$. (<i>Adapted from</i> [17]).	20
Figure 3.1 – Planning target volume (in red) and Brainstem representation (in green) in a magnetic resonance imaging (MRI) slice.	30
Figure 3.2 – m3 mMLC collimation system. <i>Courtesy Brainlab</i>	31
Figure 3.3 – LINAC-based radiosurgery system. <i>Courtesy Brainlab</i>	31
Figure 3.4 – Irradiation Plan Tab of the iPlan RT Dose 4.5 Irradiation plan. On the left, the Dyn Arc 6 is highlighted in blue and below all the corresponding parameters are displayed.	32
Figure 3.5 – Prescription dialog of the Generic Template.	34
Figure 3.6 – COIN and COIN' for Specific Template and Generic Template.	38
Figure 3.7 a), b) and c) – Representation of the cases 1, 2 and 3 belonging to Group 1, 2 and 3, respectively. The 12 Gy isodose is represented in orange.	39
Figure 3.8 a), b), c), d) – TC (%), MDPD, PITV and COIN' of the Optimized Plans vs Approved Plans.	42
Figure 3.9 – Representation of a pituitary adenoma in red, brainstem in green and optic nerves right and left in yellow.	44
Figure 3.10 – COIN, COIN' and COSI (for each critical organ) values.	45
Figure 4.1 – Brain lobes. <i>From</i> [6].	53
Figure 4.2 a), b) and c) – Sagittal, coronal and axial views.	54
Figure 4.3 – User interface overview.	55
Figure 4.4 a), b), c), d) – TC, MDPD, PITV and COIN of the Optimized Plans for each metastases location group vs Approved Plans.	60
Figure 5.1 – Kaplan-Meier analysis of overall survival.	73
Figure 5.2 – Comparison of different primary tumour locations with respect to survival.	74
Figure 5.3 – Kaplan-Meier analysis of local control.	75

Figure 6.1 – Beam’s eye view of single 130° dynamic arc for 3-mm micro-MLC (m3) showing the collimator leaves position for each 10° interval between 220°-290°.88

Figure 6.2 – Beam’s eye view of single 130° static arc for 5-mm multileaf collimator (MLC-160) showing collimator leaves position for each 10° interval between 220°-290°89

Figure 6.3 – Depth dose profiles of different field sizes for both collimator systems: a) 3×3 cm²; b) 8×8 cm².90

Figure 6.4 – Dose received by 0.1 cm³ of brainstem for a) Group III (metastases close to the brainstem) b) Group IV (meningiomas located close to the brainstem) obtained using the m3 and the MLC-160. The dashed line represents the brainstem tolerance dose, 12 Gy.....95

List of Tables

Table 2.1 – Summary of coverage and conformity indices for various treatment plans, enhancing the results obtained for the different index definitions. (<i>Adapted from [10]</i>).....	16
Table 2.2 – Summary of the dose-volume indices.....	21
Table 3.1 – Plan quality acceptability criteria.	36
Table 3.2 – Properties of the six dynamic conformal arcs for the right neurinoma Specific Template.	36
Table 3.3 – TC and MDPD indices for Specific and Generic Template.	38
Table 3.4 – Specific Template quality indices for 3 cases belonging to each of the 3 anatomic groups of neurinomas.....	39
Table 3.5 – Evaluation of the Specific Template plus mMLC adjustment in arcs 1 and 6.....	40
Table 3.6 – Average dose-volume indices values for all 19 cases of acoustic neurinoma, applying the Specific Template and with further adjustments in arc1, arcs 1 and 6 and arcs 1, 5 and 6.....	40
Table 3.7 – Average values of the dose-volume quality indices, minimum dose in the PTV and maximum dose in the brainstem for Approved treatment Plans and Optimized treatment Plans.....	43
Table 3.8 – Critical organs and corresponding tolerance doses considered at IPOCFG for SRS.....	44
Table 3.9 – COIN, COIN’ and COSI average values for approved adenoma treatment plans.....	46
Table 4.1 – Regions defined in each brain plane.	54
Table 4.2 – List of treatment templates created grouped by brain lobe location.....	56
Table 4.3 – Plan quality acceptability criteria.	57
Table 4.4 – Properties of the six dynamic conformal arcs for the right generic template and the specific template “Metastase-OCPR”.	57
Table 4.5 – Dose-volume indices for the generic template and the template “Metastase OCP” application.	58
Table 4.6 – Dose-volume indices for generic template and specific templates.....	59
Table 4.7 – Average dose-volume indices values for clinical cases of brain metastases, applying specific templates and with further adjustments in 1, 2, 3 and 4 arcs...59	59
Table 4.8 – Average values of the dose-volume quality indices for Approved treatment Plans and Optimized treatment Plans.	61
Table 5.1 – Summary of lesion characteristics and dose-volume indices.	70
Table 5.2 – Univariate survival and multivariate survival analysis.....	73
Table 6.1 – Summary of group’s characteristics.	87
Table 6.2 – Average quality indices and corresponding improvement ratios ($\pm 1\sigma$) of MLC-160 versus m3. Median values are shown in parenthesis.	93

Table 6.3 – Average values of minimum and maximum doses ($\pm 1\sigma$) to the PTV and corresponding improvement ratios for MLC-160 vs. m3. Median values are shown in parenthesis94

Table 6.4 – Brainstem sparing average values ($\pm 1\sigma$) for both collimators. Median values are shown in parenthesis.....95

Table 6.5 – Average absolute volume ($\pm 1\sigma$) of normal tissue irradiated to at least 100% of the prescribed dose, V_{NormPI} . Median values are shown in parenthesis. The fourth and fifth columns are respectively the difference in volume for the two MLCs and this volume in percentage to the PTV volume.....96

CHAPTER 1

Introduction

1.1 | Radiosurgery at IPOCFG, E.P.E.

Stereotactic radiosurgery (SRS) is a minimally invasive radiation treatment modality that delivers with high accuracy a large dose of ionizing radiation to a specific intracranial target, in a single fraction. The irradiation is based in multiple noncoplanar arcs of convergent x-rays beams.

At IPOCFG, on the day of the SRS treatment a head ring is fixed to the patient's skull under local anaesthesia. This provides a rigid fixation system that minimizes head motion and a frame of reference whereby the lesion location can be determined. After the immobilization, each patient undergoes two computed tomography (CT) scans – with and without contrast – on a dedicated big-bore CT simulator. A localization box is attached to the stereotactic head frame for imaging acquisition. The box includes tubes filled with a high-contrast material that provides easy to delineate fiducial marks. The fiducials provide a coordinate system that allows the precise determination of the position of the treatment volume with respect to the stereotactic head frame through the so called stereotactic transformation. Magnetic resonance (MR) images of the whole brain are also obtained for all patients, usually within a week before the treatment. Both CT and MR images are electronically transferred to the treatment planning system for co-registration. The neuroradiologist approves the fusion and delineates the structures, including the target lesion and the relevant organs at risk. The treatment plan is performed at the planning workstation and it is normally constituted by six or seven dynamic conformal arcs, almost always with a single isocenter per lesion. After the arcs configuration the dose distribution is computed using a pencil beam algorithm. Isodoses and further dose statistics are produced for plan evaluation.

Every time a stereotactic treatment is to be delivered, an additional collimator must be attached to the linear accelerator (LINAC) head – a micro multileaf collimator (mMLC) – with a minimum leaf width of 3 mm (m3) which allows to achieve more precise beam delivery and better definition of small fields.

Stereotactic radiosurgery demands extraordinary attention to quality assurance issues. This is related to the high accuracy required by the possible proximity of the target lesion to eloquent brain structures and to the high doses delivered. The quality control phase of the SRS treatment takes around one hour and precedes the treatment delivery. Finally, the patient is placed on the treatment couch, the target location is confirmed and the irradiation takes place.

Figure 1.1 summarizes the basic steps of a SRS treatment at IPOCFG.

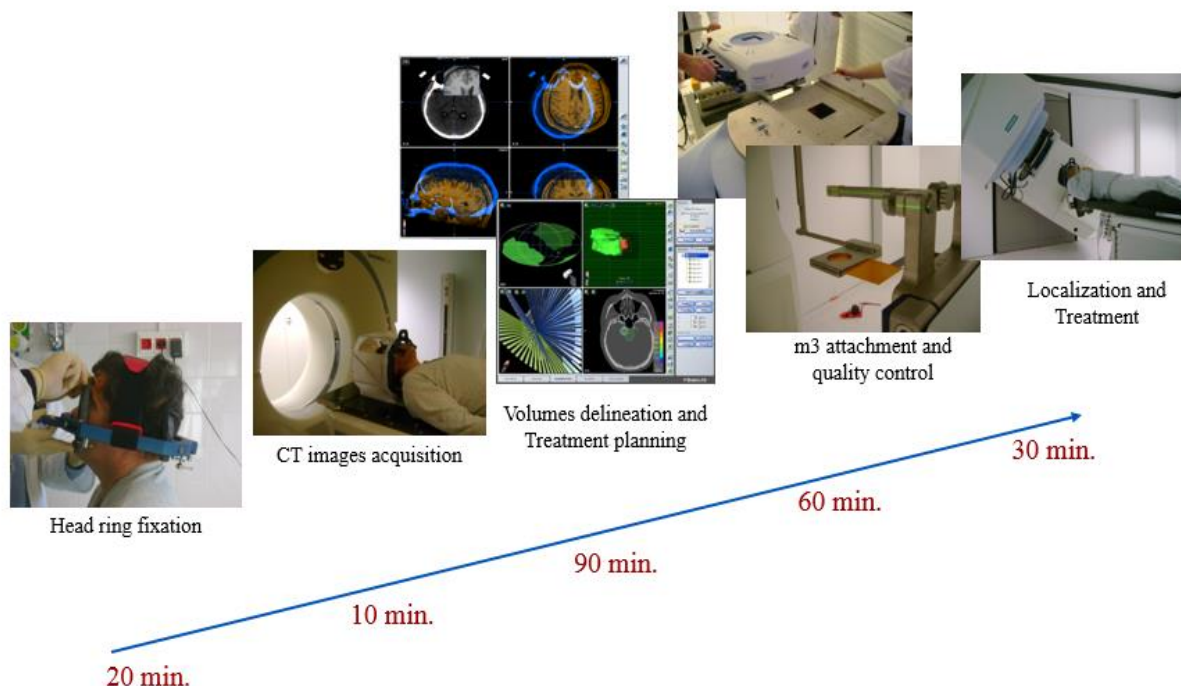


Figure 1.1 – The basic steps of a SRS treatment at IPOCFG.

This project focuses on the treatment planning phase, where the irradiation strategy is designed in order to accomplish the treatment dose prescription.

1.2 | Motivation and Goals

At IPOCFG, the treatment planning uses a generic template (defined with 6 dynamic arcs) just differing in position for right or left lesions with no adjustments for the tumour type or specific location of the lesion in the brain. For each specific clinical case, the plan optimization includes the need to determine the optimal arc properties. Subsequently, the conformity of the dose distribution to the target volume is accomplished through a time consuming process where for each arc the mMLC leaves are manually adjusted.

The main goals of this project were twofold: i) first to configure the treatment parameters according to the tumour type and location in order to create templates that speed up and optimize the treatment planning process; ii) from the casuistic of the lesions treated with SRS at IPOCFG to evaluate the quality loss if the micro-multileaf

collimator (minimum leaf width of 3 mm) used for SRS was replaced by an integrated multileaf collimator with 160 leaves (5 mm leaf width) on the linear accelerator.

1.3 | Organization of the Dissertation

This dissertation results from the compilation of a set of self-consistent papers, written in English, all with an underling thread on optimizing procedures in stereotactic radiosurgery. The five resulting papers have been written along the 10 months of the MSc. project carried out at the Medical Physics Department of IPOCFG:

- I. Dose-volume Quality Indices for Radiosurgery Treatment Plan Assessment: A review. (Submitted to *Acta Radiológica Portuguesa*)
- II. Definition and evaluation of a template to speed up radiosurgery treatment planning of acoustic neurinoma. (Electronic Poster presentation at the 3rd *ESTRO Forum*, 24-28 April 2015, Barcelona, Spain)
- III. Stereotactic Radiosurgery for the treatment of brain metastases: definition and evaluation of templates to speed up treatment planning. (Manuscript)
- IV. Stereotactic Radiosurgery of brain metastases: analysis of outcome. (Submitted to *Acta Neurochirurgica*)
- V. Dosimetric comparison of multileaf collimator systems for intracranial stereotactic radiosurgery (Submitted to *Physica Medica*)

The self-consistency of each paper implied some redundancy mainly in the introductory paragraphs that could not be avoided.

The quality of radiosurgery treatment plans is assessed through the calculation of dose-volume indices. These indices are a complementary and powerful tool that facilitate decisions during the dosimetric comparison of various treatment plans. The definition of these indices progressed over the last decades as demonstrated by the number of papers that can be found in the literature. In order to summarize the quality indices defined for radiosurgery treatment plan assessment, a comprehensive review was made – Paper I (Chapter 2).

To get used with the treatment planning system while aiming at following the first objective of the project, specific templates for right and left acoustic neurinomas were developed and evaluated in terms of plan quality – Paper II (Chapter 3).

A retrospective planning study was also made to develop specific templates with adjustments for different metastatic lesions locations, to evaluate their quality and to determine the minimum number of arcs where the mMLC shape must be adjusted for the treatment plans to comply with the local acceptability criteria. For the latter task, a simple brain mapping has been considered and a user-friendly graphical interface was developed in order to assist the planner in choosing the adequate specific template – Paper III (Chapter 4).

The casuistic study of all brain metastases treated at IPOCFG from March 2008 to December 2014 and a treatment outcome evaluation, identifying the factors that may influence the overall survival and the local control were made. These analyses have been slightly off the main objectives of this project, however, they gave me a clear idea about the patients and the characteristics of the treated lesions as well as an evaluation of the outcome associated with this treatment technique and a comparison with the results reported by other institutions. Moreover they have allowed me an interesting and useful contact with some biostatistics methods and tools – Paper IV (Chapter 5).

Finally, the quantitative evaluation, in terms of plan quality losses, of the eventual replacement of the 3 mm micro MLC by a 160 MLC with 5 mm leaf width was carried out as a support study to that management decision – Paper V (Chapter 6).

Dose-volume Quality Indices for Radiosurgery Treatment Plan Assessment: A Review

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Abstract

Dose-volume quality indices measure the homogeneity of the dose distribution, the coverage of the target by the prescription isodose surface and the conformity of the prescription isodose to the target volume. The definition of these indices progressed over time being the conformity indices those that evolved the most. They became highly sophisticated evolving from just volumetric definitions to definitions that take into account the organs at risk affection, the size and shape of the target volume or the dose gradient outside the target volume.

The search for such useful tools has been continuous along the last decades as demonstrated by the number of papers that can be found in the literature concerning this issue. A comprehensive review on the quality indices defined for radiosurgery treatments assessment is presented.

2.1 | Introduction

Stereotactic radiosurgery (SRS) is a minimally invasive treatment technique where high doses of radiation are delivered in a single fraction with high accuracy to a small and well-defined target. Targets are commonly small intracranial lesions [1].

SRS combines the principles of stereotaxy (from Greek: “stereo” – three-dimensional space, “taxy” – localization) for localization of target volume with multiple collimated beams of focused high energy photon radiation. This creates a steep dose gradient in the borders of the target that allows a selective damage of tumours and a maximum protection of healthy tissues [1,2].

Because SRS is a highly focused treatment, it is useful in situations where the tumour is small (the larger dimension shall not exceed 3 cm) and contained into a localized area [2]. Malign tumours (metastatic brain tumours, gliomas, ependymomas, medulloblastomas), benign tumours (neurinomas, meningiomas, pituitary tumours) and non tumour pathologies such as arteriovenous malformations are indicated for SRS treatment. Also, SRS may be used as a complementary treatment in case of residual lesions, recurrent small sized lesions of the brain or as a local “boost” at the end of the conventional external beam radiation therapy [1,2].

2.1.1 | Evolution of Radiosurgery

Horsely and Clark [3] were the first to create an apparatus for defining brain locations with Cartesian coordinates, in 1908. In 1951 the Swedish neurosurgeon Leksell introduced the Radiosurgery concept [4].

There are three basic forms of SRS represented by three different technological instruments: Gamma Knife, Linear accelerator (LINAC) and systems that accelerate heavy particles as protons (cyclotrons or synchrotrons).

In the late 1960's, Leksell and Larsson [5] developed a system named Gamma Knife. This system was constituted by 179 sources of Cobalt-60 and the gamma radiation was focused in a target stereotaxically localized. Gamma Knife systems suffered multiple modifications over the years and systems with 201 sources are presently the most used.

LINAC-based radiosurgery systems were first proposed by Betti and Derechinsky [6] in 1984 and a year after by Colombo et al. [7]. Betti and Derechinsky's system used circular collimators of different diameters coupled to the linear accelerator and the SRS treatment was achieved with multiple convergent and noncoplanar arcs. Since then, linear accelerator-based SRS has become highly sophisticated, evolving from circular arc and multiple isocenters per target to dynamic conformal arcs usually based on a single isocenter.

The dynamic conformal arc irradiation technique uses a micro-multileaf collimator (mMLC) to conform the radiation beam to the target volume every 10 degrees. The capacity of continuous dynamic movement of the leaves and the continuous conformation to the target volume during irradiation, allow improving the conformity and homogeneity of the dose distribution in irregular targets [8].

In 1962, at the Massachusetts General Hospital in Boston, Kjelleberg [9] presented a proton beam-based radiosurgery system. This system used protons of 150 MeV produced by a synchrotron. Proton beams deposit more energy as they slow down, culminating in an absorption peak (the Bragg peak). This allows the majority of the radiation dose to be delivered to the target site and significantly reduce the dose to normal tissues near the target.

2.1.2 | Radiosurgery Treatment Assessment

For evaluating a treatment plan the visual inspection of the dose distribution image by image still is one of the most important and used methods. Another helpful tool for evaluating plan quality and compare competing plans are dose-volume-histograms. Dose-volume-histograms summarize the dose and volume statistics for delineated structures and give information on the volume of a given structure that receives a particular dose. However, when comparing different plans, dose-volume-histograms may contain large amounts of data which make the comparison difficult and time consuming. So, multiple plans of treatment can more easily be compared through the use of quality indices. Probably the most cited parameters to classify radiosurgery treatment plans are the so called indices of conformity and coverage [10]. Indices of this type were defined for the first time in 1993 by the Radiation Therapy Oncology Group (RTOG) [11].

2.2 | Dose-volume quality indices: definitions and discussion

2.2.1 | Coverage Indices

RTOG in 1993 [11] was the first to propose a coverage index defined as a ratio between doses:

$$\text{Coverage (RTOG)} = \text{TC} = \frac{D_{min}}{pi} \quad 2.1$$

where D_{min} is the minimum dose in the target volume and pi is the prescribed isodose value. TC stands for Target Coverage.

A value of TC equal to 1.0 corresponds to an ideal coverage (the target volume completely covered by the prescription isodose surface); when the value is between 0.9-1 the treatment plan is considered to comply with the protocol; when TC is in the range 0.8-0.9 the protocol violation is considered to be minor, and if TC is below 0.8 the protocol violation is considered to be major.

If the target volume is located adjacent to a critical organ which has normally a tolerance dose lower than the therapeutic dose for the tumour, for protecting the critical

organ it may be necessary to underdose a small volume of the target. In this case, the minimum dose in the target may be low in a small volume, but coverage may be acceptable which is not taken into account in the coverage index defined by RTOG [10].

Lomax and Scheib in 2003 [10] presented a new definition of coverage that solved this problem. That new coverage index definition is a relation between volumes:

$$TC (\%) = \frac{V_{T,pi}}{V_T} \times 100\% \quad 2.2$$

where $V_{T,pi}$ is the volume of target that receives at least the prescription dose and V_T is the target volume as shown in Figure 2.1.

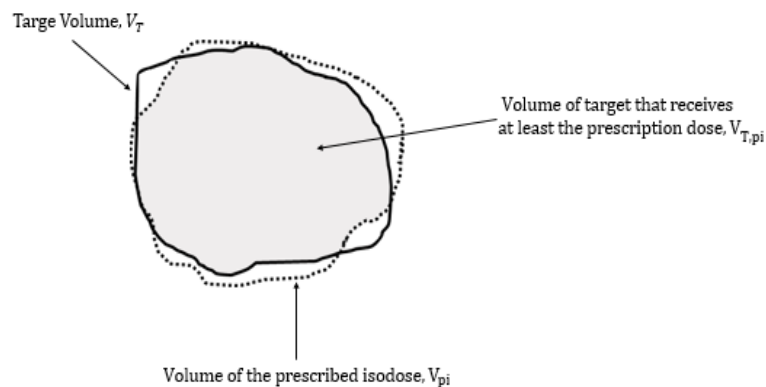


Figure 2.1 – Definition of the volumes used in dose-volume quality indices. The solid line shows the target volume, V_T ; the dotted line shows the prescription isodose, p_i ; represented in grey is the volume within the target receiving at least the prescription isodose, $V_{T,pi}$.

Ideally, TC will be 100%. The aim is a $TC \geq 95\%$, but the acceptable coverage depends on the clinical indication and on the position of the target thus while for a benign lesion a coverage between 90%–95% may be acceptable, for the treatment of metastases, the coverage should be close to 100%.

2.2.2 | Homogeneity Indices

RTOG in 1993 [11] defined an index, Homogeneity Index (HI) or Maximum Dose to Prescribed Dose (MDPD) that helps to evaluate the homogeneity of the dose distribution:

$$\text{HI (MDPD)} = \frac{D_{\max}}{pi} \quad 2.3$$

where D_{\max} is the maximum dose in the target volume and pi is the prescribed isodose value. MDPD should be less than 2.0. If this occurs, the treatment plan is considered to comply with the protocol. When this index is between 2-2.5 there is a minor protocol violation, and when it is above 2.5 the protocol violation is considered to be major, though the plan might still be considered as acceptable.

2.2.3 | Conformity Indices

Several different conformity indices have been proposed to describe the conformity of the prescription isodose to the target volume. PITV ratio, proposed by RTOG in 1993 [11] is defined as the total volume enclosed by the prescription isodose divided by the target volume:

$$\text{PITV} = \frac{V_{pi}}{V_T} \quad 2.4$$

where V_{pi} is the volume of the prescribed isodose and V_T is the target volume as shown in Figure 2.1. A value of 1.0 would indicate a perfect conformation. A value between 1 and 2 indicates that the plan is considered to comply with the protocol; $2 \leq \text{PITV} \leq 2.5$ or $0.9 \leq \text{PITV} \leq 1.0$ indicate a minor deviation, and $\text{PITV} \leq 0.9$ or $\text{PITV} \geq 2.5$ would correspond to a major deviation.

Nedzi et al. in 1993 [12] used a conformity index called Treatment Volume Ratio (TVR) which was defined as the ratio of the target volume to the treatment volume (volume of prescription isodose). This index is the inverse of PITV. Knöös et al. in 1998 [13] proposed the Radiation Conformity Index (RCI) that is again the inverse of PITV.

A Conformity index was also defined in the ICRU 62 Report [14] in 1999 from previous RTOG recommendations. In this definition it was imposed that “the planning target volume (PTV) is fully enclosed by the treated volume (reference isodose volume)”. This means that 100% coverage is assumed and there, the conformity index is defined as the ratio between the treated volume (reference isodose volume) and the planning target volume (target volume).

These conformity indices are simply a ratio between volumes and do not consider the location or shape of the prescription isodose relatively to the target volume. So, a perfect conformity score could eventually be obtained with a prescription isodose surface not at all, or only partly, overlapping the target volume, contributing to a significant dose to normal tissues [10].

In 1997, Van't Riet et al. [15] presented the Conformation Number (CN). This index basically combines two ratios: the proportion of the target covered by the prescription isodose (equivalent to TC) and the proportion of the prescription isodose volume that covers the target, as follows:

$$CN = \frac{V_{T,pi}}{V_T} \times \frac{V_{T,pi}}{V_{pi}} \quad 2.5$$

where CN is the conformation number, having a value between 0 and 1. When CN is 1 the conformation is ideal. Van't Riet et al. suggested that plans may be considered conformal if they have a CN greater than 0.6.

In 1998, the definition of CN was renamed as COIN (Conformity Index) by Baltas et al. [16]. COIN is the product between the CN and a factor that takes into account the dose received by critical organs. So, when there are no critical organs near the target volume, COIN is equal to CN and can be written as:

$$COIN = \frac{[V_{T,pi}]^2}{V_{pi}V_T} \quad 2.6$$

When there are critical organs near the target volume, COIN will be named COIN' taking into account the degradation of its value:

$$COIN' = COIN \prod_{i=1}^N \left[1 - \frac{V_{COref}^i}{V_{CO}} \right] \quad 2.7$$

The product factors are defined for each critical organ i , where V_{COref} is the volume of the critical organ (CO) that receives at least the prescription dose and V_{CO} the volume of that critical organ.

However, COIN' only refers to the fractional volume of critical organ receiving the prescription dose or higher which deserves two important remarks. The first is that it mixes information about target coverage, normal tissue irradiation and specific critical organs, and it is impossible to distinguish the contribution of each term to the resultant COIN' value. The second is that COIN' only accounts for critical organ volumes receiving prescription doses and higher. In many cases, critical organ tolerances are lower than tumour prescription doses and this is not considered about this restriction [17].

Paddick in 2000 [18] proposed a conformity index (CI_P) that is basically equal to CN and in 2001 it was modified by Nakumura et al. [19] and presented as the inverse of the initial index (CI_N).

Lomax and Scheib in 2003 [10] suggested a Conformity Index (CI) that solved the PITV problem of geographic miss. This new index was defined as the ratio of the volume of target receiving at least the prescription dose, to the volume enclosed by the prescription isodose.

$$CI = \frac{V_{T,pi}}{V_{pi}} \quad 2.8$$

CI scores the normal tissue overdose, however, it does not contain complete information about the target coverage, and different quality plans can have identical CI values. For example, if the prescription isodose is completely enclosed in the target volume, the CI score will be 1 although the plan would not obviously be ideal (See case 3, Table 2.1) [10].

COIN, CN and CI should be greater than 0.6 for the plan to be consider conformal [10,15,16].

Table 2.1 – Summary of coverage and conformity indices for various treatment plans, enhancing the results obtained for the different index definitions. (*Adapted from [10]*)

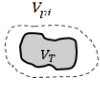



Treatment Plan /Case	Volumes (cm ³)	TC(%) ^[10]	PITV ^[11]	RCI ^[13]	CN=COIN=CI _p ^[15,16,18]	CI _N ^[19]	CI ^[10]
1 	V _T =2.0 V _{pi} =4.0 V _{T,pi} =2.0	100%	2.0	0.5	0.5	2.0	0.5
2 	V _T = 2.0 V _{pi} =2.6 V _{T,pi} =1.8	90%	1.3	0.77	0.62	1.27	0.69
3 	V _T =2.0 V _{pi} =1.0 V _{T,pi} =1.0	50%	0.5	2.0	0.5	1.0	1.0
4 	V _T = 2.0 V _{pi} =2.0 V _{T,pi} =1.0	50%	1.0	1.0	0.25	4.0	0.5

Table 2.1 shows four simplified treatment plans and summarizes the different proposed dose-volume indices. In Case 1 the target volume is completely enclosed in the prescription isodose surface and so, the target coverage is perfect. However, there is a poor conformity as shown by all conformity scores (CN, CI, PITV, RCI, CI_N). In Case 2 the prescription isodose surface is slightly shifted towards the left of the target volume, therefore the target coverage is worse than in Case 1, but the conformity is much better because a less amount of healthy tissue receives the prescription dose. In Case 3 the prescription isodose is completely enclosed in the target volume which will give a perfect CI score although the poor conformity of the isodose shape relatively to the target volume enhances the failure of this definitions. Indeed if CI is used alone it will be misleading because it does not contain complete information about the target coverage. On the other hand, CN index includes a target coverage factor which is accounted by the low score. In Case 4, the target volume and the volume of the prescribed isodose are equal but slightly apart and therefore PITV is 1 in spite of conformity is not clearly good. This reflects the PITV geographic miss but, CN and CI overcome this PITV problem and show the lack of conformity.

A study made by Wu et al. [20] demonstrated that currently used conformity measures, namely the PITV, would provide misleading results of the quality of a treatment plan when examining small target sizes or complex shapes. PITV tends to have higher values for smaller or more complex targets even when the prescription isodose coverage is equivalent to other plans for larger volumes or simpler shapes.

To overcome this limitation, the authors Wu et al. [20], proposed a Distance-based Conformity Index (CDI) that is independent of the target size and shape and in which the conformity of the prescription isodose to the target volume is measured as the average distance between the surfaces of the target and the prescription isodose, as follows:

$$CDI = \frac{(V_{pi} - V_{T,pi}) + (V_T - V_{T,pi})}{\frac{1}{2} \times (S_T + S_{pi})} \quad 2.9$$

where S_T is the surface of target and S_{pi} the surface of prescription isodose. For calculating the target and prescription isodose surfaces, Wu et al. approximated the target and prescription isodose volumes to ellipsoids. For each target, they measured the major axes to get the elongation ratio and then calculated the volume. However, if the volume has a very irregular shape this approximation will not be good.

An important feature of radiosurgery is the steep dose gradient outside the target volume. An index that gives a measure of the dose falloff outside the target – Conformity/Gradient Index (CGI) – was proposed by Wagner et al. [21] in 2003. The CGI was defined as the average of two terms, a conformity score (CGIc) and a gradient score (CGIg) given as follows:

$$CGIc = 100 \times \frac{V_T}{V_{pi}} \quad 2.10$$

$$CGIg = 100 - \{100 \cdot [(R_{Eff,50\%pi} - R_{Eff,pi}) - 0.3 \text{ cm}]\} \quad 2.11$$

where $R_{Eff, pi}$ is the effective radius of the prescription isodose volume and $R_{Eff,50\%pi}$ is the effective radius of the 50% isodose volume.

The effective radius of a volume is the radius of a sphere of equal volume, and is calculated as:

$$R_{Eff} = \sqrt[3]{\frac{3V}{4\pi}} \quad 2.12$$

The final CGI index value is given by:

$$CGI = (CGIc + CGIg)/2 \quad 2.13$$

A $CGIg \geq 100$ corresponds to an optimum 3 mm or steeper gradient (distance between the prescription and the 50% isodoses effective radii). This ideal 3 mm gradient was obtained empirically from radiosurgery planning cases, and corresponds to the gradient that is possible with LINAC radiosurgery when using multiple noncoplanar arcs and small circular collimators (<20 mm) [21].

CGIg score scales linearly with differences in effective dose shell radii, for example, when $CGIg = 90$ the effective gradient is 4 mm, when $CGIg$ is 80 the effective gradient is 5 mm, and so forth.

The CGI increases with plan desirability or quality, such that an ideal plan with $CGIc = 100$ and $CGIg = 100$ would have a CGI score of 100. As either the conformity or the gradient worsens, $CGIc$ or $CGIg$ decreases, and the CGI score therefore decreases [21].

However, the CGI does not address the issue of dose homogeneity within the target volume. CGI also does not consider the radiation dose to radiosensitive structures other than non-target brain tissue. Maximizing CGI score allows minimizing the quantity of healthy tissue that receives high doses ($\geq 50\%$ of the prescription dose). So, the probability of not having treatment complications is maximized but just when all of the non-target volume is of about the same radiosensitivity. When there are different radiosensitivities (highly or less radiosensitive structures) near the target volume, CGI does not provide information about doses to these radiosensitive structures [21].

In 2006, Paddick [22] proposed another index to evaluate the steep dose gradient outside the target volume – Gradient Index (GI). The GI is defined as the ratio of the volume of the 50% isodose to the volume of the prescription isodose:

$$GI = \frac{V_{50\%pi}}{V_{pi}} \quad 2.14$$

This index can be used to compare treatment plans of equal conformity but with different dose gradients. A smaller value of GI reflects a steeper dose gradient and, therefore, a lower irradiation of healthy tissues. This is particularly useful in critical anatomical locations or larger volumes where the GI helps to select the dose plan with the lowest “penumbra dose” and particularly important for multi-isocenter treatments, which are used in the majority of Gamma Knife dose plans [22].

In 2006, Menhel et al. [17] proposed a new index that allows distinguishing between different critical organs, Critical Organ Scoring Index (COSI). This new index considers the target coverage and critical organ irradiation:

$$COSI = 1 - \frac{V(CO)_{>tol}}{TC_V} \quad 2.15$$

where $V(CO)_{>tol}$ is the fraction of volume of the critical organ (CO) receiving more than its tolerance dose, and TC_V is the volumetric target coverage, defined as the fractional volume of target volume covered by the prescription isodose.

COSI yields a false perfect score if the critical organ is completely spared, regardless of tumour coverage. When COSI is < 1 it is impossible to know if this is due to a poor target coverage or to an overdosage of the critical organ. This loss of information is actually present in any of the conformity indices that account for more than one factor, either coverage and conformity or for multiple organs [17].

To overcome these problems and facilitate the choice of an optimal treatment plan, the same authors, proposed a two-dimensional representation of COSI versus Conformity Index (CI), where CI is the index proposed by Lomax and Scheib (Eq.8).

The combination of CI and COSI compensates both for the loss of information contained in the definition of COSI and CI when each is used separately, and for the potential false perfect scores that COSI yields. Thus, if $COSI = 1$ due to a complete organ sparing, but the target coverage is poor, this will be reflected in a low CI value [17]. The advantage of a two dimensional representation is demonstrated in Figure 2.2.

In Figure 2.2 a hypothetical case of three different plans is presented, with one target volume and one CO to be assessed.

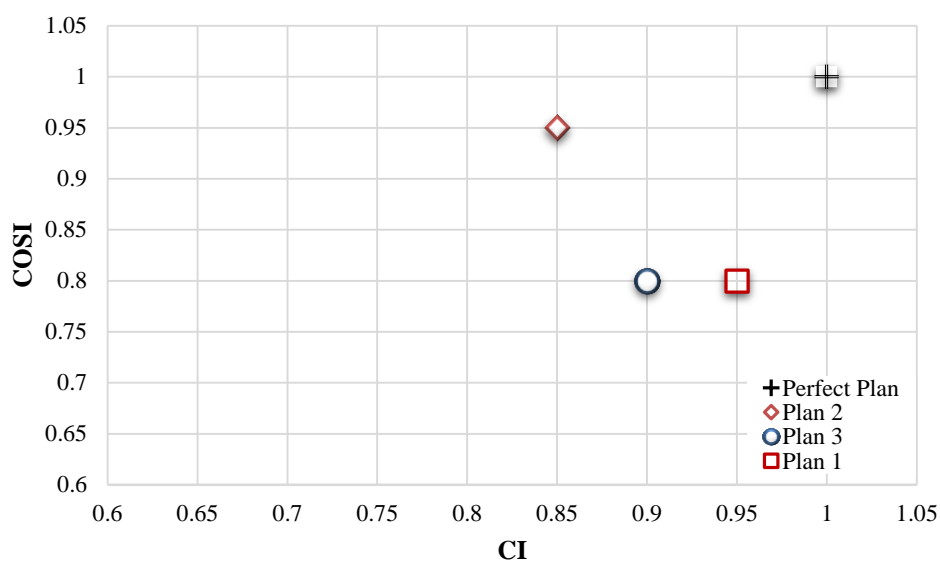


Figure 2.2 – COSI vs CI for three different plans and one critical organ. Each plan is a point in the plane. The Perfect plan scores at $COSI=CI=1$. (Adapted from [17]).

The ‘+’ denotes an ideal plan, with a perfect target coverage, perfect conformity and full critical organ sparing. Plan 1 is the best in terms of conformity (conformity index of 0.95). Plan 2 is the best in terms of critical organ sparing. Plan 1 and Plan 3 have the same COSI but they may not spare the critical organ on the same amount. Through the analysis of CI and TC definitions ($CI = V_{T,pi}/V_{pi}$ and $TC = V_{T,pi}/V_T$), it is possible to express CI as $\frac{TC \times V_T}{V_{pi}}$. As Figure 2.2 shows, CI of Plan 1 is greater than CI of Plan 3, and this can be due to a greater target coverage or to a smaller prescription isodose volume. If the target coverage of Plan 1 is greater than the target coverage of Plan 3, for COSI in the two plans to be the same, the fraction of critical organ in Plan 1 that receives more than its tolerance dose should be greater than that fraction in Plan 3 and so, the critical organ in Plan 1 is less spared than in Plan 3.

In case of Plan 2, CI is lower than in Plans 1 and 3 but COSI is higher. As CI and COSI are 0.85 and 0.95 the target coverage is necessary high although lower than in the other plans and so, the organ sparing should be the best of all three plans.

All three plans have acceptable CI and COSI values, so the choice will probably depend on what type of critical organ is being assessed and whether organ sparing is more important than target conformity or vice versa.

Table 2.2 summarize the discussed dose-volume indices.

Table 2.2 – Summary of the dose-volume indices.

RTOG ^[11] , 1993	$TC = \frac{D_{min}}{pi}$ $MDPD = \frac{D_{max}}{pi}$ $PITV = \frac{V_{pi}}{V_T}$	D_{min} : Minimum Dose pi : Prescription Isodose Value D_{max} : Maximum Dose V_{pi} : Prescription Isodose Volume V_T : Target Volume
Van't Riet et al. ^[15] , 1997	$CN = \frac{V_{T,pi}}{V_T} \times \frac{V_{T,pi}}{V_{pi}}$	$V_{T,pi}$: Volume of the target that receives at least the prescription isodose
Baltas et al. ^[16] , 1998	$COIN = \frac{[V_{T,pi}]^2}{V_{pi}V_T}$ $COIN' = COIN \prod_{i=1}^N [1 - \frac{V_{COref}^i}{V_{CO}}]$	V_{CO} : Volume of a critical organ V_{COref} : Volume of the critical organ that receives at least the prescription isodose
Lomax and Scheib ^[10] , 2003	$TC (\%) = \frac{V_{T,pi}}{V_T} \times 100\%$ $CI = \frac{V_{T,pi}}{V_{pi}}$	
Wu et al. ^[20] , 2003	$CDI = \frac{(V_{pi} - V_{T,pi}) + (V_T - V_{T,pi})}{\frac{1}{2} \times (S_T + S_{pi})}$	S_T : Target surface S_{pi} : Prescription isodose surface
Wagner et al. ^[21] , 2003	$CGI = (CGIc + CGIg)/2$ $(1) CGIc = 100 \times \frac{V_T}{V_{pi}}$ $(2) CGIg = 100 - \{100 \cdot [(R_{Eff,50\%pi} - R_{Eff,pi}) - 0,3 \text{ cm}]\}$	$R_{Eff,pi}$: Effective radius of the prescription isodose volume $R_{Eff,50\%pi}$: Effective radius of the 50% isodose volume
Paddick ^[22] , 2006	$GI = \frac{V_{50\%pi}}{V_{pi}}$	$V_{50\%pi}$: Volume of the 50% isodose
Menhel et al. ^[17] , 2006	$COSI = 1 - \frac{V(CO)_{>tol}}{TC_V}$	$V(CO)_{>tol}$: Fraction of volume of the CO receiving more than its tolerance dose TC_V : the volumetric target coverage

Other approaches for evaluating treatment plans that were not discussed here are Normal Tissue Complication Probability (NTCP), Tumour Control Probability (TCP) and more recently Equivalent Uniform Dose (EUD). The advantage of this type of indicators over the purely dosimetric dose-volume indices is that they attempt to incorporate radiobiology, and thus they are more intuitively related to the treatment outcome but they are out of the scope of the present paper [17].

2.3 | Conclusion

Indices for evaluating the quality of a radiosurgery plan can facilitate decisions during the dosimetric comparison of various treatment plans. They allow choosing the plan that provides the best compromise in terms of coverage, conformity and homogeneity because multiple parameters can be easily analysed. Dose-volume indices

allow not only the evaluation of the quality of the different treatment plans, but also facilitate the comparison between various available techniques and technologies, because these influence the geometry of the dose distributions.

The ideal solution to the problem of plan evaluation would be an index that could both integrate all the relevant data and present it in a simple and quantitative form, but unfortunately such ideal tool does not exist. Namely because the treatment plan evaluation will always be a multiple criteria problem. As it has been discussed, each previous definition includes some drawbacks that may hide out some important features of the dose distribution either concerning the target or the healthy surrounding structures.

In order to harmonize definitions and also to save planning time, it would be important that the treatment planning systems could include some of the needed tools to calculate these indices. Such implementation would enable the users to choose the suitable quality indices and include them in the approved plan documentation along with the details of the dose calculations, tending to comply with reporting level 3 according to ICRU 83 recommendations [23].

2.4 | References

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**Definition and evaluation of a template to
speed up radiosurgery treatment planning of
acoustic neurinomas**

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Abstract

Purpose: A Generic Template with no specific adjustments for tumour type is used at IPOCFG for linear accelerator-based radiosurgery treatment planning. It involves further manual adjustments of the micro-multileaf collimator (mMLC) leaves in all the generic arcs for improving the treatment plan quality which is a cumbersome task. The purpose of this work is to present specific templates for right and left acoustic neurinomas and compare their performance with the Generic Template in terms of plan quality, and to determine the minimum number of arcs where the mMLC shape must be adjusted for the treatment plan to comply with the local acceptability criteria.

Methods and Materials: The treatment plans of twelve cases of right acoustic neurinomas treated at IPOCFG were analysed. From this retrospective study, a Specific Template for right acoustic neurinoma was created and the Specific Template for left acoustic neurinoma was defined as precisely the mirror of the right template. In total, nineteen cases involving acoustic neurinomas have been re-planned with the Specific Template (right or left) and their plan quality assessed. Treatment planning was conducted using the iPlan RT Dose planning system, version 4.5 from BrainLAB. The target volumes ranged from 0.265-7.523 cm³ (mean: 2.085±1.772 cm³) and the prescribed dose was 12-14 Gy (mean: 12.15±0.50 Gy). Treatment plans were generated using 6 dynamic conformal arcs and their quality evaluation was assessed through the calculation of dose-volume indices and dose distribution analysis.

Results: The Specific Template performed better than the Generic Template in terms of conformity (COIN=0.558±0.034 for the Specific Template and COIN=0.547±0.034 for the Generic Template) and critical organ sparing (COIN[']=0.554±0.031 for the Specific Template and COIN[']=0.538±0.031 for the Generic Template). The coverage and the homogeneity of the dose distribution were similar for both: TC=0.981±0.007, MDPD=1.065±0.013 for the Specific Template and TC=0.984±0.007, MDPD=1.067±0.013 for the Generic Template.

Conclusion: Applying the proposed Specific Template for acoustic neurinoma, the compliance to local acceptance quality criteria was achieved with manual correction of the mMLC leaves for just two of the six dynamic arcs used for treatment. This represented a considerable reduction – to around 1/3 – of the treatment planning time, accomplishing the purpose of the present work which was speeding up the treatment planning phase in radiosurgery without jeopardizing the plan quality.

3.1 | Introduction

Acoustic neurinomas (vestibular schwannomas) are benign and slow-growing tumours that develop in the myelin sheath of the vestibular branch of the VIII cranial nerve. As the tumour grows, it expands from its origin inside the internal auditory canal out into the space between the brainstem and the temporal bone known as the cerebellopontine angle. The pear-shaped tumour can continually enlarge, compressing the trigeminal nerve and can eventually compress the brainstem. Acoustic neurinomas represent approximately 10% of all brain tumours, they are slightly more common in women and appear at an average age of 50 years old. Symptoms include unilateral sensorineural hearing loss of variable degrees, instability, vertigo, tinnitus, headache and even facial numbness [1,2].

The cause of acoustic neurinoma is largely unknown. They can be sporadic (in 95% of the time) or caused by an inherited condition called neurofibromatosis type 2. Neurofibromatosis type 2 origin acoustic tumours in both left and right sides – bilateral acoustic tumours [1].

As acoustic neurinomas are benign and slow growing tumours an immediate treatment may not be necessary if patient has few symptoms. The option to observe every year these tumours until they grow or symptoms change is a possible approach [2].

Historically, treatment options have included total or subtotal surgical tumour resection that evolved for micro-surgical methods. For healthy patients with symptomatic unilateral tumours, surgical resection has been considered the standard treatment. However, some patients are elderly or medically infirm (patients that have a tumour in the only ear, bilateral acoustic neurinomas, post-surgical recurrence) and others reject surgery. Furthermore, the location of these tumours at the skull base in close proximity to multiple critical neurological structures (cranial nerves, brainstem) leads to appreciable surgical morbidity. Presently a well-established alternative to surgical resection in the case of small and medium-sized acoustic neurinomas (< 3cm) is stereotactic radiosurgery (SRS). This technique ensures an acceptable control rate and low rate of neuro-otological complications. Conventional radiotherapy is not used in acoustic neurinoma treatment, although there exists some evidence of its efficacy [2].

The aims of radiosurgery and surgery are different. Surgery aims at totally remove the tumour while radiosurgery intention is to stop the tumour growing by inducing avascular necrosis leading to collagen deposits [2,3].

The first radiosurgical treatment of an acoustic neurinoma was proposed in 1969 and was carried out in 1971 [3].

At IPOCFG, the radiosurgery treatment of neurinomas is linear accelerator (LINAC)-based. The technique is based in dynamic conformal arcs (DCA) rotating about a single isocenter using a micro-multileaf collimator (m3 mMLC) to conform to the target volume.

The treatment planning uses a Generic Template (just defined as right or left 6 arc template) with no specific adjustments for neurinomas and so, for each clinical situation, the physicist needs to determine which arc properties are the optimal. This is a non-trivial problem, especially because the brainstem is anatomically close to the target. Additionally, the conformity of the dose distributions is further accomplished through a time consuming process where for each arc the mMLC leaves are manually adjusted for each sub-incidence, every 10 degrees.

The aims of this work were to develop and evaluate in terms of plan quality a Specific Template for cases of acoustic neurinoma (right and left) with optimized arc parameters and prescription details, as well as to determine the minimum number of arcs where the mMLC shape must be adjusted for the treatment plan to comply with the local acceptability criteria.

3.2 | Methods and Materials

3.2.1 | Target Lesions

Clinical records of 19 patients with acoustic neurinoma that underwent SRS between 23 January, 2013 and 21 May, 2014 formed the basis of this retrospective study. These 19 patients have in total 12 right-sided lesions, 6 left-sided lesions and 1 bilateral lesions ranging in volume from 0.265 to 7.523 cm³ (mean: 2.085±1.772 cm³). The dose prescribed to the planning target volume (PTV) ranged from 12 to 14 Gy (mean: 12.15±0.50 Gy).

3.2.2 | Organ at Risk

Acoustic neurinomas grow and expand from their origin to the space between the brainstem, therefore in the radiosurgery treatment planning the brainstem is considered as the important organ at risk (see Figure 3.1).

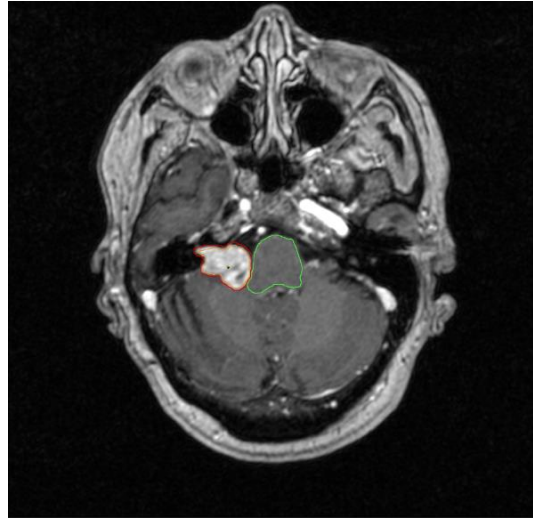


Figure 3.1 – Planning target volume (in red) and Brainstem representation (in green) in a magnetic resonance imaging (MRI) slice.

From QUANTEC (Quantitative Analysis of Normal Tissue Effects in the Clinic) compilation, Sharma et al. in 2008 [4] reported that exposing the brainstem to more than 12 Gy produces new neurological deficits. Mayo et al. in 2010 [5] suggested that a maximum brainstem dose of 12.5 Gy is associated with low (<5%) risk.

At IPOCFG 12 Gy is considered the brainstem's tolerance dose.

3.2.3 | Treatment Technique

SRS is performed using the mMLC of BrainLab, with full advanced integration in a Siemens Oncor Avant-Garde linear accelerator using the 6 MV photon mode. The mMLC has 26 pairs of leafs: from centre to periphery, 14 pairs have 3 mm width, 6 pairs have 4.5 mm width and 6 pairs have 5.5 mm width – Figure 3.2. It is a tertiary or additional collimator which must be attached to the LINAC head every time a stereotactic treatment is to be delivered – Figure 3.3.



Figure 3.2 – m3 mMLC collimation system. *Courtesy Brainlab.*



Figure 3.3 – LINAC-based radiosurgery system. *Courtesy Brainlab.*

The irradiation technique is based on 6 or 7 dynamic conformal arcs, always with a single isocenter for each lesion.

During irradiation, the gantry is rotating while the leaves of the mMLC move according to the beam's eye view (each leaf of the mMLC moves linearly at 10° intervals interpolating from the initial position to the next calculated position). The capacity of continuous dynamic movement of the leaves and the continuous conformation to the target volume during the irradiation, allow improving the conformity and the homogeneity of the dose distribution for irregular targets.

3.2.4 | Treatment planning

Treatment planning is conducted using computed tomography (CT), contrast-enhanced magnetic resonance (MR) images and the iPlan RT Dose planning system, version 4.5 from BrainLAB.

MR images are fused with planning CT images using iPlan RT Image version 4.1.1 (BrainLAB). Then, the neuroradiologist approves the image fusion and delineates the gross tumour volume (GTV) and the brainstem on the MR images. Subsequently, the planning target volume (PTV) is defined as the GTV plus an isotropic margin of 1mm incorporating the clinical target volume (CTV) and accounting for setup errors and other possible isocenter localizing uncertainties.

The treatment plan is normally constituted by 6 dynamic conformal arcs defined by the parameters: table position, gantry start, gantry stop, collimator angle, weight and margin as Figure 3.4 shows. The treatment planning software creates a field shape using the m3 that conforms to the outline of the PTV plus a predefined margin of 3mm in the beam's eye view in the starting position of the arc and for every 10° sub-arcs.

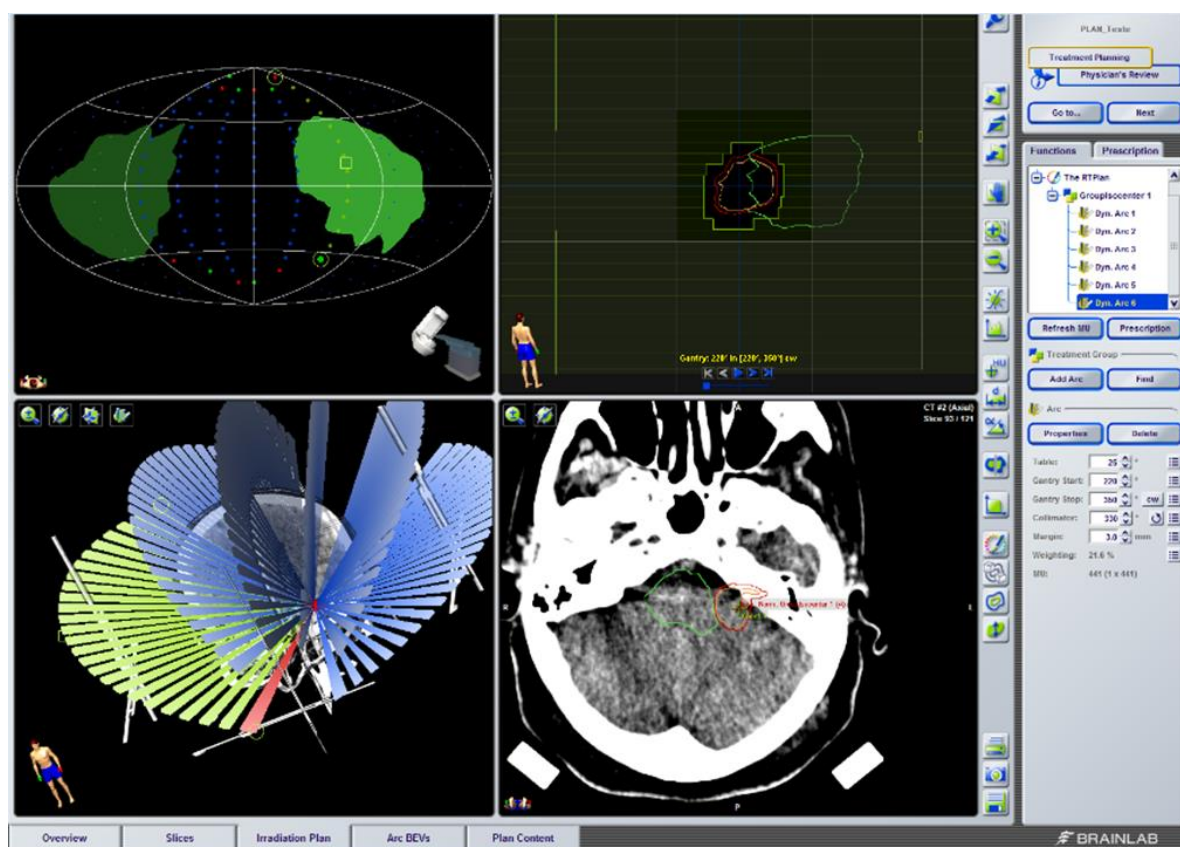


Figure 3.4 – Irradiation Plan Tab of the iPlan RT Dose 4.5 Irradiation plan. On the left, the Dyn Arc 6 is highlighted in blue and below all the corresponding parameters are displayed.

Figure 3.4 shows the Irradiation Plan Tab in iPlan. The upper left view, the collision map, shows a two-dimensional view of the segmented objects as projected onto a spherical surface: brainstem localization in green and the arcs representation in blue. The isocenter is positioned at the centre of the view. The beam eye view (upper

right view) shows the GTV (orange contour), the PTV (red contour), the brainstem (green contour), and the m3 leaves of arc 6 in 160 degrees gantry position are represented.

The shapes of the defined arcs concentric at the PTV (in red) are shown in the three-dimensional (3D) overview (lower left view). The slice view (lower right view) displays the brainstem contour (in green) and the PTV and GTV in red and orange, respectively.

On the bottom left of every view, an icon indicates the orientation of the patient position. The orientation of the patient icon helps to verify from what angle the four views display the respective object. The view orientation in the 3D views is displayed in accordance with the position of the gantry and table. The table/gantry icon in the bottom right of the collision map indicates the positions of the gantry and the treatment table.

To define a treatment plan the Functions and the Prescription tabs are used [6].

a) Functions Area

The Functions tab shows different buttons and spin boxes.

Table, Gantry and Collimator spin boxes allow changing the numeric value of the treatment table angle or the starting and stopping points of the gantry in an arc.

The margin spin box allows to assign a margin (in millimetres) to the PTV geometrical conformation by the mMLC leaves for an individual arc. In order to achieve the required dose falloff and to compensate for the penumbra region, a sufficient margin should be given. Normally a 2–3 mm mMLC margin is added around the PTV.

The weighting spin box allows to define the weighting (in percentage) for each arc. Weighting determines the percentage of the dose that the arc delivers to the PTV, and thus the number of monitor units (MU) calculated for the respective arc [6].

The treatment plan usually includes six dynamic conformal arcs: two dynamic conformal arcs on the opposite side of the lesion, three in the same side of it and one corresponding to a cranial incidence as Figure 3.4 presents.

b) Prescription Area

The treatment prescription is generically defined by the number of treatment fractions (1 fraction in the case of SRS), the prescription dose (in Gy) and the

restrictions that are imposed to limit the dose to the organs at risk (OAR) and other normal tissues. Figure 3.5 shows the Prescription Dialog window.

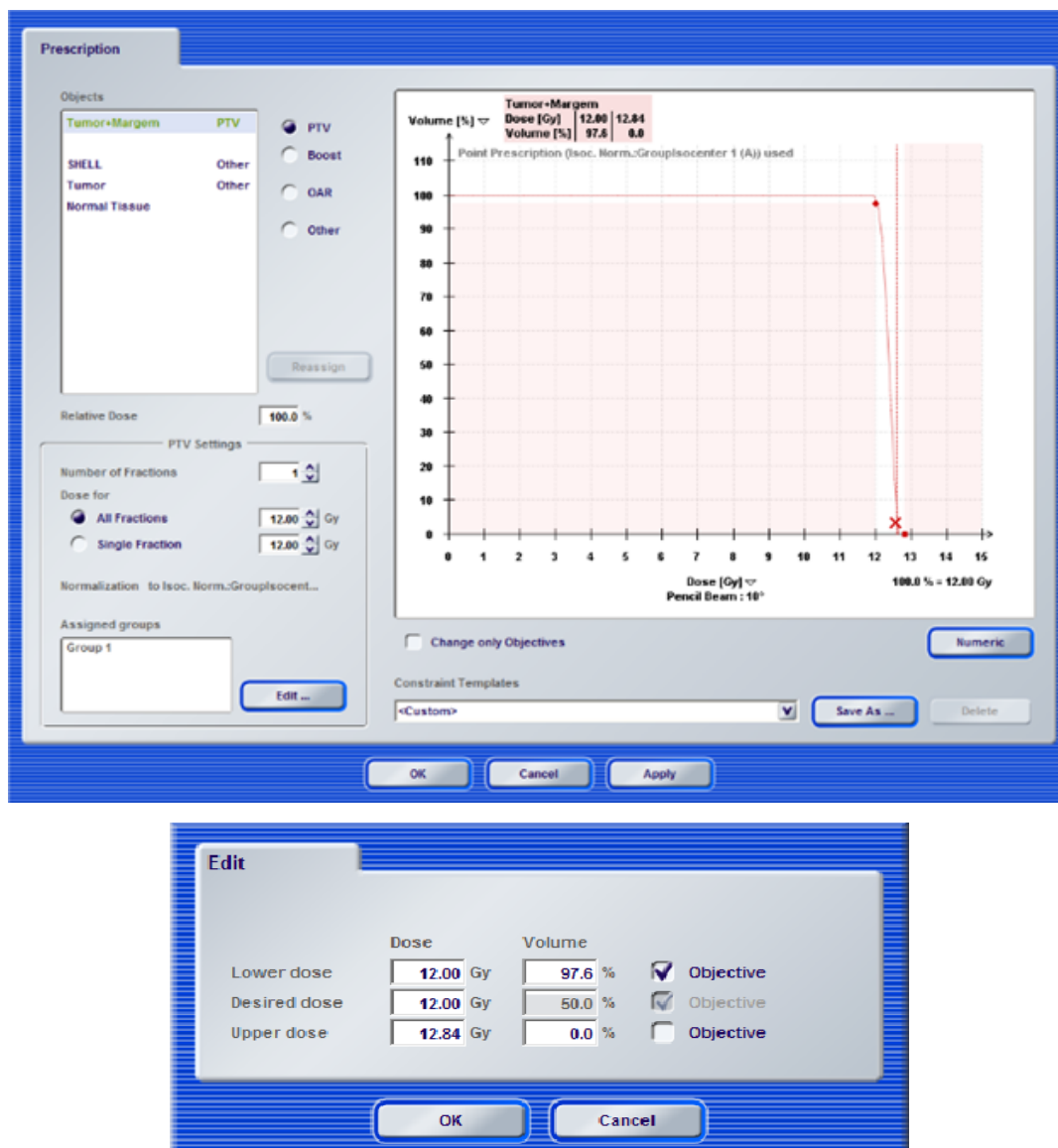


Figure 3.5 – Prescription dialog of the Generic Template.

To the left side of the Prescription dialog window the Objects list is presented containing all visible objects. To the right of this list, there is an Object Type options area. Here an object is defined as either *PTV*, *Boost*, *OAR Type 1*, *OAR Type 2*, *OAR Type 3* or *Other* object. OAR type 1 provides the maximum protection for the respective organ at risk, whereas OAR type 3 does not have an influence on the leaf adaptation, but provides the dose-volume-histogram (DVH) constraint information on the respective object in the DVH dialog. If an object is defined as OAR type 2, the system

evaluates the respective location with respect to the PTV during leaf optimization. The result can be, for example, that small parts of the PTV margin are covered by a leaf in order to protect the corresponding area of the OAR.

To the right of the Object Type list, there is the graph area that displays the DVH of the object highlighted in the Objects list.

Bellow the graph, there is a Numeric button that opens the Adjust dialog window where the dose-volume constraints can be defined. Bellow the Object Type options area, the percentage of the dose for a particular volume, the number of fractions and the prescribed dose are defined. The dose display options are valid for the entire treatment plan [6].

In the Generic right or left Templates – Figure 3.5, the brainstem is not considered as an organ at risk. Their prescription just defines the tumour as a PTV and imposes that 97.6% of the PTV should receive the prescription dose.

3.2.5 | Treatment plan Evaluation

The treatment plan quality evaluation is accomplished through the calculation of dose-volume indices, the visual inspection of the dose distribution image by image and the analysis of the DVHs for the different structures, namely the minimum dose in the PTV ($D_{\text{Min(PTV)}}$), the maximum dose in the brainstem ($D_{\text{Max(BS)}}$) and the volume of the brainstem that receives more than its tolerance dose (this volume is named as $V_{12 \text{ Gy(BS)}}$).

The dose-volume indices assess the homogeneity of the dose distribution – MDPD (ratio between maximum dose and the prescribed dose) [7] – the coverage of the target by the prescription isodose surface – TC (target coverage) [8] – and the conformity of the prescription isodose to the target volume – PITV (ratio of the prescription isodose surface volume to the target volume) [7] and COIN (conformity index) [9]. They have been reviewed in a former paper [10].

For a treatment plan to be acceptable, it must meet the criteria shown in Table 3.1.

Table 3.1 – Plan quality acceptability criteria.

Parameter	Value
TC	$\geq 95\%$
COIN	≥ 0.6
PITV	≥ 1 & ≤ 2
MDPD	≥ 1 & ≤ 2
$D_{\text{Min(PTV)}}$	$\geq 95\% \times \text{Prescribed Dose}$
$D_{\text{Max(BS)}}$	≤ 12 Gy
$V_{12\text{Gy(BS)}} (\text{cm}^3)$	as low as possible and usually $\ll 0.1$ cc

3.2.6 | Specific Template Creation

Through the retrospective analysis of the approved treatment plans for all patients with right neurinoma, a right template with six dynamic conformal arcs was created. Template definitions are shown in Table 3.2. The left template (for left neurinomas) was defined afterwards with precisely the mirrored values for table position, collimator position, gantry start and gantry stop. The prescription is the same for the two templates.

Table 3.2 – Properties of the six dynamic conformal arcs for the right neurinoma Specific Template.

Table	Gantry Start	Gantry Stop	Collimator	Weigthing
10	230	350	320	18.6%
37	220	340	320	16.5%
64	210	340	300	13.4%
90	200	340	270	10.3%
300	150	20	60	19.6%
335	140	10	45	21.6%

The Specific Template prescription defines the tumour as a PTV and the brainstem as an organ at risk type 3. PTV's dose-volume constraints impose that 97.6% of the volume must receive the prescription dose and that the maximum dose must be less than 107% of the prescribed dose. In the dose-volume constraints of the brainstem 12 Gy is considered the tolerance dose.

To improve the conformity between the target volume and the prescription isodose and so sparing healthy tissues and protecting the brainstem, manual adjustments still have to be made in the mMLC shape. In the Generic Template these

adjustments are made in all the arcs which is a very time consuming task. Arcs weighting determines the dose percentage that each beam delivers to the PTV. The most heavy arcs impact significantly the dose distribution and so, for speeding up the radiosurgery treatment planning, after the Specific Template application, the mMLC leaves were adjusted just in the heaviest arcs, arc 1, arcs 1 and 6 and arcs 1, 6 and 5, and the plans quality were successively assessed.

The treatment plan quality was evaluated through the use of the same methods referred in page 35. Critical Organ Scoring Index (COSI) proposed by Menhel et al. [11] and COIN' which is a derivation of COIN that takes into account the degradation of its value when there are critical organs near the target volume were also calculated. These indices evaluate the brainstem sparing. For a plan to be considered conformal both indices should be greater than 0.6.

3.3 | Results and Discussion

A comparison between the Specific Template and the Generic Template was made to demonstrate the advantages in terms of plan quality of using the Specific Template instead of the Generic Template and so, to validate its development. The two templates were independently applied and the direct plan quality provided by each one was assessed with no adjustments made in the mMLC shape.

In Figure 3.6, COIN index average values reflect that the Specific Template provides a better conformity than the Generic Template, on average, for the studied clinical cases and the COIN' index average values indicate that the Specific Template is better in terms of critical organ sparing, as expected because the Generic Template does not consider the brainstem as an organ at risk. Although the Generic Template ignores the presence of the brainstem, the templates difference in terms of organ at risk sparing is not large because the prescription dose and the brainstem tolerance dose are both equal to 12 Gy.

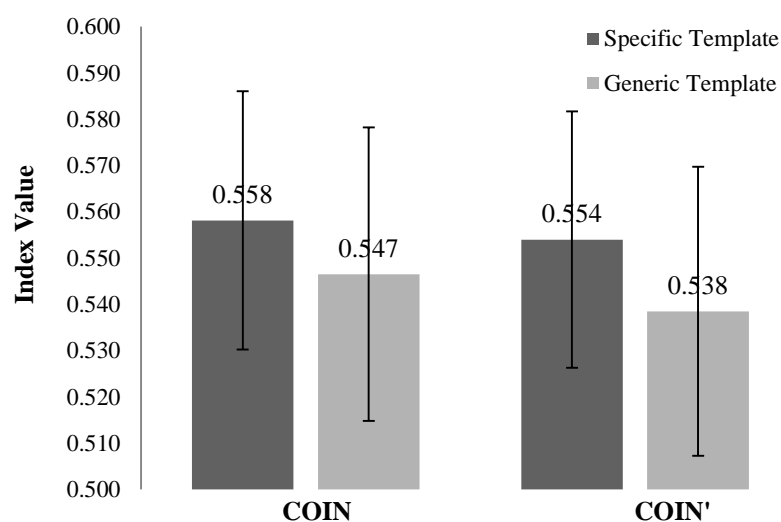


Figure 3.6 – COIN and COIN' for Specific Template and Generic Template.

The target coverage (TC) and the dose distribution homogeneity (MDPD) are similar for both as Table 3.3 shows.

Table 3.3 – TC and MDPD indices for Specific and Generic Template.

Index	Specific Template	Generic Template
TC	0.981±0.007	0.984±0.007
MDPD	1.065±0.013	1.067±0.013

The treatment plans achieved with the Specific Template, for the studied clinical cases, can be divided into three groups according to the lesion localization that lead to similar quality indices in each group. Group 1 includes lesions that compress the brainstem (minimum distance between the brainstem and the lesion is 0 mm) and that have volumes larger than 3.5 cm³. Group 2 includes lesions that are far from the brainstem (the brainstem and the lesion minimum distance is between 1.5 mm and 15.2 mm) but that have irregular shapes. Lesions that are very close (minimum distance less than 1.0 mm) or compress the brainstem and that have volumes smaller than 2.7 cm³ belong to Group 3. To illustrate the group's characteristics three cases randomly selected from each group are presented in Figure 3.7.

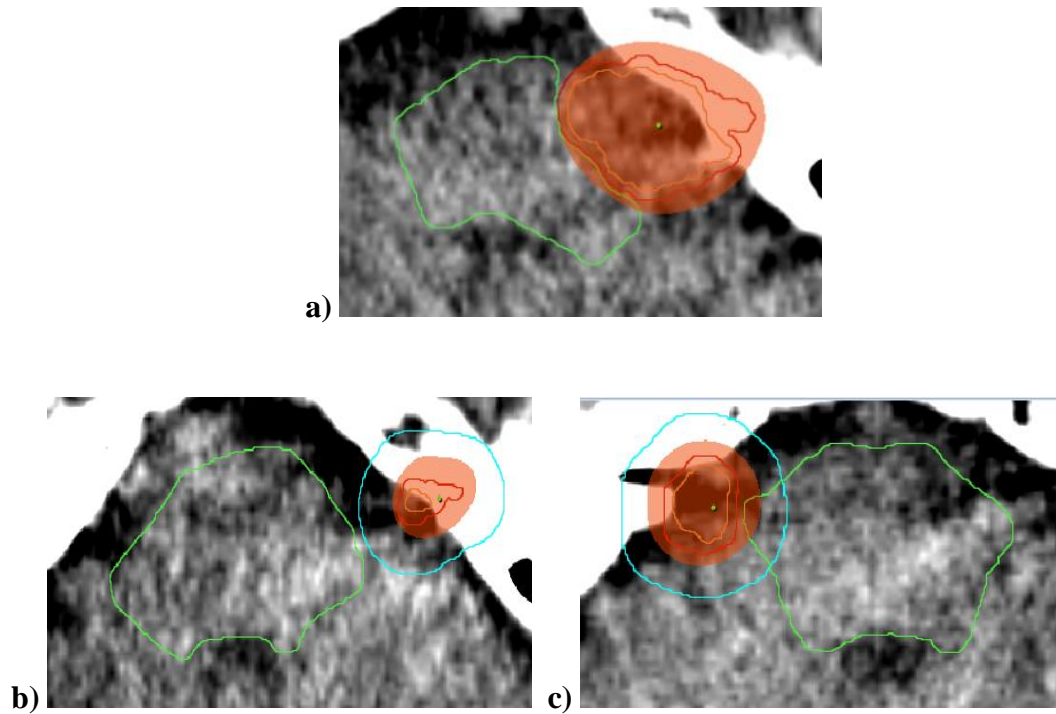


Figure 3.7 a), b) and c) – Representation of the cases 1, 2 and 3 belonging to Group 1, 2 and 3, respectively. The 12 Gy isodose is represented in orange.

Table 3.4 shows the Specific Template evaluation for these three cases. Indices that accomplish the criteria are shown in green, otherwise they are in red.

Table 3.4 – Specific Template quality indices for 3 cases belonging to each of the 3 anatomic groups of neurinomas.

Case	TC	MDPD	PITV	COIN	COIN'	COSI	$D_{\min}(\text{PTV})$ (Gy)	$D_{\max}(\text{BS})$ (Gy)	$V_{\text{BS}(>12\text{Gy})}$ (cm^3)
1	0.981	1.070	1.565	0.615	0.592	0.963	11.540	12.520	0.375
2	0.979	1.074	1.700	0.563	0.563	1.000	11.550	6.60	0.000
3	0.988	1.078	1.738	0.562	0.550	0.979	11.58	12.600	0.169

In Case 1 target coverage, conformity and homogeneity are in concordance with the plan acceptability criteria presented in the Table 3.1, but the maximum dose in the brainstem is greater than its tolerance dose (12 Gy) due the lesion localization. In this case, the mMLC leaves adjustment will improve the brainstem protection. In Case 2, COIN indicates that conformity is poor due to the form of the lesion, but the maximum dose received by the brainstem is lower than its tolerance dose because the neurinoma is sufficiently away from this organ at risk. The adjustment of mMLC leaves, mainly reducing the template margin will improve the conformity quality. In Case 3 besides

the poor conformity, the maximum dose in the brainstem and the volume that receives at least 12 Gy are high, therefore the mMLC leaves adaptation will also improve the plan quality.

After the Specific Template application the mMLC leaves were adjusted in the heaviest arcs: successively arc 1, arcs 1 and 6 and arcs 1, 6 and 5.

With mMLC adjustments in arc 1 the conformity increases and the fraction of brainstem that receives at least 12 Gy decreases. However, COIN and COIN' for Case 2 still do not comply with the plan acceptability criteria. The compliance was achieved with manual correction of the mMLC leaves in arcs 1 and 6. Adjustments in these arcs improved conformity, homogeneity and organ sparing but the target coverage slightly decreased –Table 3.5.

Table 3.5 – Evaluation of the Specific Template plus mMLC adjustment in arcs 1 and 6.

Case	TC	MDPD	PITV	COIN	COIN'	COSI	$D_{\min}(\text{PTV})$ (Gy)	$D_{\max}(\text{BS})$ (Gy)	$V_{\text{BS}(>12\text{Gy})}$ (cm^3)
1	0.974	1.071	1.267	0.750	0.735	0.980	11.540	12.390	0.193
2	0.982	1.072	1.547	0.623	0.623	1.000	11.560	6.660	0.000
3	0.981	1.073	1.409	0.683	0.675	0.989	11.550	12.480	0.092

Corrections in arcs 1, 5 and 6, further enhances the plan quality for the three cases. To understand if the improving of quality indices with increasing the number of arcs where the mMLC is manually adjusted is actually a trend, the average value of each dose-volume index was calculated and presented in Table 3.6, for successive manual adjustments in arc 1, arcs 1 and 6 and arcs 1, 5 and 6.

Table 3.6 – Average dose-volume indices values for all 19 cases of acoustic neurinoma, applying the Specific Template and with further adjustments in arc1, arcs 1 and 6 and arcs 1, 5 and 6.

	TC	MDPD	PITV	COIN	COIN'	COSI
Specific Template	0.981±0.007	1.065±0.013	1.732±0.558	0.558±0.034	0.554±0.031	0.992±0.011
+ adj. in Arc 1	0.981±0.006	1.064±0.012	1.574±0.134	0.615±0.047	0.611±0.044	0.993±0.010
+ adj. in Arcs 1,6	0.979±0.006	1.063±0.012	1.464±0.101	0.658±0.044	0.654±0.041	0.995±0.007
+ adj. in Arcs 1,6,5	0.979±0.006	1.062±0.012	1.430±0.093	0.672±0.043	0.667±0.041	0.995±0.007

As it is shown in the table, the direct application of the Specific Template yields treatment plans that comply on average with the plan acceptability criteria in terms of

coverage and homogeneity. However, the conformity is poor as COIN and PITV reflect.

The adjustment of the mMLC shape is clearly useful for improving the conformity. The mMLC adjustment in arc 1 allows, on average, an increase of 10% in COIN and a decrease of 9% in PITV (the ideal PITV value is 1) leading to COIN values that comply with the plan acceptability criteria. The mMLC adjustment in arcs 1 and 6 improves in 18% the COIN and in 15% the PITV and the adjustment in arcs 1, 5 and 6 increases COIN in 20.4% and decreases PITV in 17.4%, on average. COIN' values show a substantial increase of the brainstem sparing with mMLC adjustments. As the brainstem tolerance dose and the prescribed dose are equal for acoustic neurinomas, the COSI index does not have any advantage relatively to COIN' in this study. The critical organ affectation, if it exists, is so low that the COSI is always close to 1. However, COSI definition advantages are evident in other clinical cases as for instance in pituitary adenomas (see Appendix).

The target coverage (TC) tends to decrease with the increasing of the number of arcs where the mMLC shape is adjusted, which is expected as the adjustment tends to cover regions where the PTV and the brainstem are close or adjacent. The homogeneity of the dose distribution given by the index MDPD is not significantly affected by the mMLC adjustments and can even slightly improve with it.

The manual adjustment of the mMLC shape is a cumbersome task that slows down the treatment planning phase in radiosurgery. Therefore knowing the minimum number of arcs on which the mMLC shape adjustment may produce an acceptable plan is a very significant and useful information. The presented results show a strong evidence that the correction of the mMLC shape in just arcs 1 and 6, which are usually the ones with the higher weights, leads to treatment plans that comply with the acceptability plan criteria. To further corroborate this conclusion, Figure 3.8 presents the dose-volume indices corresponding to the Specific Template plus adjustment of the mMLC in arcs 1 and 6 – named Optimized Plans – versus the same indices for the Approved Plans with corrections in all arcs.

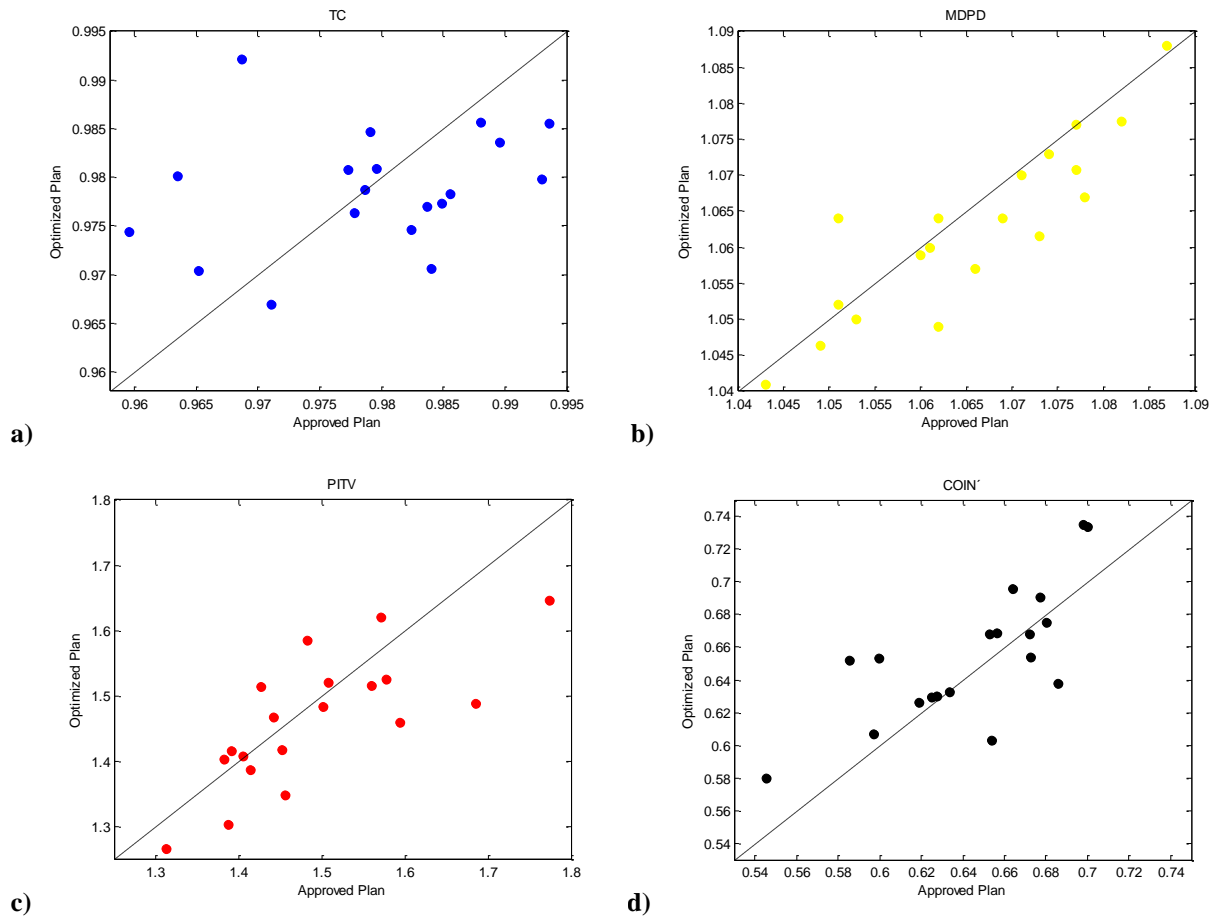


Figure 3.8 a), b), c), d) – TC (%), MDPD, PITV and COIN' of the Optimized Plans vs Approved Plans.

Dashed lines have a slope equal to 1, so they represent equivalent results for both plans. If the points are above the dashed line for the TC and COIN' representation and below the dashed line for the PITV and MDPD representations, the Optimized Plan with just two adjusted arcs and having the Specific Template as a starting point is better than the Approved Plan. All points below the dashed line for the TC and COIN' representation and above the dashed line for the MDPD and PITV representation are cases where the Optimized Plan could not achieve the Approved Plan quality.

Figure 3.8 a), b), c), d) confirm that the correction of the mMLC shape in just two arcs produce treatment plans that in general respect the plan acceptability criteria. In 8/19 cases the target coverage (TC) of the Optimized Plan is equal or greater than the target coverage of the Approved Plan and it is always greater than 95% (the minimum acceptable value). In terms of conformity, in 14/19 cases COIN' of the Optimized Plan is equal or greater than COIN' of the Approved Plan and the PITV of the Optimized Plan is less than the PITV of the Approved Plan in 11/19 cases. MDPD is better in the Optimized Plan in 14/19 cases. PITV and MDPD are always less than

2.0 and therefore plans are acceptable according to these indices. COIN' should be greater than 0.6 but in four of the Approved Plans it is less than this limit. Nevertheless this occurs in just one Optimized treatment Plan.

To summarize the comparison between Approved and Optimized Plans, the average values of the dose-volume quality indices, minimum dose in the PTV and maximum dose in the brainstem were calculated and presented in Table 3.7.

Table 3.7 – Average values of the dose-volume quality indices, minimum dose in the PTV and maximum dose in the brainstem for Approved treatment Plans and Optimized treatment Plans.

	Approved Treatment Plan	Optimized Treatment Plan
TC	0.98±0.01	0.98±0.01
MDPD	1.07±0.01	1.06±0.01
PITV	1.49±0.01	1.46±0.10
COIN	0.65±0.04	0.66±0.04
COIN'	0.64±0.04	0.65±0.04
COSI	1.00±0.01	1.00±0.01
$D_{\min}(\text{PTV})$	11.80±0.50 Gy	11.79±0.50 Gy
$D_{\max}(\text{BS})$	10.11±3.47 Gy	10.35±3.44 Gy

On average, for equal coverage, Optimized Plans are more homogeneous and conformal at the expenses of a slightly non-significant underdosage of the PTV (minimum dose of 1 cGy less) and a slightly overdosage of the brainstem (maximum dose of 24 cGy more) without exceeding its tolerance dose.

3.4 | Conclusions

The Generic Template standardly used at IPOCFG in the treatment planning of acoustic neurinomas treated with radiosurgery does not have specific adjustments for the tumour type and when it is applied, the optimization of the treatment plan to reach the acceptance criteria according to the local treatment protocol is a hard and time consuming task. The proposed specific templates (right or left) for acoustic neurinoma define the brainstem as an organ at risk and allow to have a better conformity just from the starting point. These represent a great advantage in terms of improving and speeding up the radiosurgery treatment planning phase.

The Specific Template application with further adjustment of the mMLC leaves conformation in just two arcs, arcs 1 and 6, allows obtaining a treatment plan quality

that respect the plan acceptability criteria and in some cases with better indices than the approved treatment plans where the mMLC shape is adjusted in all arcs. This optimization reduces to around 1/3 the treatment planning time and so, the purpose of this work was fully accomplished.

3.5 | Appendix: COIN' vs COSI for pituitary adenomas

Pituitary adenomas are relatively common brain tumours, representing 10-20% of all primary intracranial tumours [12]. Microsurgery and fractionated radiotherapy are historically the eligible treatment modalities but it has been demonstrated that radiosurgery offers a viable treatment for recurrent or residual pituitary adenomas [12].

Between December 2012 and December 2014, 8 pituitary adenomas were treated with SRS at IPOCFG. The mean prescribed dose for these lesions was 16.3 ± 1.5 Gy. Optical nerves, brainstem and chiasm were considered as organs at risk in treatment planning due to their proximity to adenomas location – Figure 3.9. The corresponding tolerance doses are presented in Table 3.8.

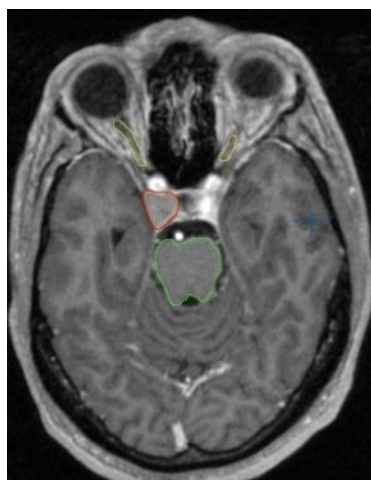


Figure 3.9 – Representation of a pituitary adenoma in red, brainstem in green and optic nerves right and left in yellow.

Table 3.8 – Critical organs and corresponding tolerance doses considered at IPOCFG for SRS.

Critical Organ	Tolerance Dose (Gy)
Brainstem	12
Chiasm	8
Optic Nerves	9

COIN' definition considers the volume of each critical organ that receives at least the prescription dose but mixes information about target coverage, normal tissue irradiation and specific critical organs, being thus impossible to distinguish the contribution of each factor (see Chapter 2, page 19). Otherwise, COSI is calculated for each critical organ considering the volume of each critical organ that receives more than its tolerance dose. Figure 3.10 presents the COIN, COIN' and COSI (C=Chiasm; BS=brainstem; RON=right optical nerve and LON=left optical nerve) values for three different treated cases, to illustrate the use of COSI.

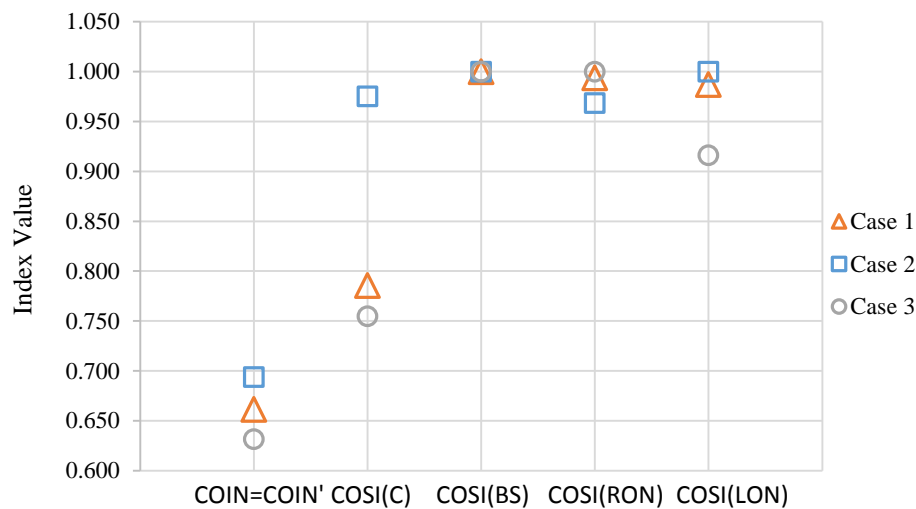


Figure 3.10 – COIN, COIN' and COSI (for each critical organ) values.

COIN and COIN' values for the presented clinical cases of pituitary adenomas are equal for each of the three cases, indicating that the critical organs have been mostly spared. Nevertheless the sparing linked to COIN' concerns just prescribed doses which in the cases of adenomas may be considerably higher than the tolerance dose of the proximal critical organs. Indeed COSI values reveal how effectively the different organs at risk have been affected. In Case 1 and Case 3 the right optic nerve and the brainstem are mostly spared whereas for these two cases the chiasm was the organ at risk with the lowest dose protection, which derives from being the organ with the lowest tolerance dose. Concerning the left optic nerve, it is completely spared in Case 2 whereas for Case 3 it is clearly affected in some extension. Overall, for these three examples of adenomas, we can say that Case 2 is the one with better sparing of the four considered organs at risk.

Organs at risk affectation depends of the clinical situation as for example the lesion volume, prescribed dose and lesion location. Table 3.9 presents the COIN, COIN' and COSI average values for all clinical cases.

Table 3.9 – COIN, COIN' and COSI average values for approved adenoma treatment plans.

COIN	COIN'	COSI(C)	COSI(BS)	COSI(RO)	COSI(LON)
0.593±0.077	0.593±0.077	0.888±0.129	0.999±0.001	0.989±0.014	0.976±0.040

COSI average values reflect that chiasm is the organ at risk mostly affected, as illustrated for the three clinical cases previously presented. Table 3.9 presents average values, but in a given clinical case, different treatment plans can be compared on the basis of the calculated values of COSI for each critical organ to help the physician's decision on the best plan for treatment.

In the clinical cases of pituitary adenomas COSI definition advantages have thus been demonstrated which was not so obvious for the previous described case of neurinomas.

3.6 | References

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**Stereotactic Radiosurgery for the treatment
of brain metastases: definition and evaluation of
templates to speed up treatment planning**

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Abstract

Purpose: At IPOCFG, a generic template with no specific adjustments for tumour type neither for its brain location is used for linear accelerator based radiosurgery treatment planning. The purpose of this retrospective planning study was to present specific templates with adjustments for different metastatic lesions locations, compare their performance with the generic template in terms of plan quality and to determine the minimum number of arcs where the micro-multileaf collimator (mMLC) shape must be adjusted for the treatment plan to comply with the local acceptability criteria.

Methods and Materials: From this retrospective study, a plain brain mapping was considered and a specific template developed for each defined brain region (15 in total). Cases involving brain metastases treated from October 2012 to August 2014 have been re-planned with the appropriate specific template and their plan quality assessed through the calculation of dose-volume indices and dose distribution analysis. Due to the high number of specific templates created, a user-friendly graphical interface was developed to help the specific template choice. Treatment planning was conducted using the iPlan RT Dose planning system, version 4.5 from BrainLAB.

Results: The specific templates provide, at the starting point, better conformity and homogeneity of the dose distribution than the generic template (COIN= 0.561 ± 0.040 and PITV= 1.725 ± 0.129 for the generic template and COIN= 0.564 ± 0.039 and PITV= 1.716 ± 0.132 for the specific templates). Target coverage is similar for both: TC= 0.978 ± 0.003 for the generic template and TC= 0.978 ± 0.004 for the specific templates.

Conclusion: Specific templates for brain metastases allow to achieve treatment plans compliance with the local plan acceptability criteria with manual correction of the mMLC leaves for just three arcs of the 6/7 dynamic arcs used for treatment. This contributes for a reduction of the treatment planning time to around 1/2-1/3 without compromising the plan quality.

4.1 | Introduction

Brain metastases smaller than 3cm in diameter represent the most common indication for stereotactic radiosurgery (SRS) [1]. SRS delivers a high dose of radiation to precisely defined intracranial lesions in a single fraction, using multiple convergent beams usually describing multiple dynamic concentric arcs. This contributes to a high and uniform dose to the target volume while minimizing the irradiation of the surrounding normal tissue which allows the treatment of brain metastases in any location, including inside the brainstem [1].

Several randomized trials reported that SRS extends overall survival and accomplishes highly effective and predictable local control, for single and multiple brain metastases even for radioresistant metastases from melanoma or renal cancer [2-4].

The treatment planning uses a generic template (defined with 6 dynamic arcs) just differing in position for right or left lesions with no adjustments for the specific location of the lesion in the brain. For each specific clinical case, the plan optimization includes the need to determine the optimal arc properties. Due to the diversity of possible locations of brain metastases as they can appear in any brain location, even in close proximity to critical structures as brainstem and optic chiasm, this is not a simple task. The conformity of the dose distributions is further accomplished through a time consuming process where for each arc the mMLC leaves are manually adjusted for each sub-incidence, every 10 degrees.

The purpose of this work was to create a specific template for each defined brain region, to evaluate its quality and to determine the minimum number of arcs where the mMLC shape must be adjusted for the treatment plan to comply with the local acceptability criteria. For the latter task, a simple brain mapping has been considered and a displaying tool was developed in order to assist the planner in choosing the adequate specific template.

4.2 | Methods and Materials

4.2.1 | Target Lesions

A retrospective analysis of the treatment plans of 81 patients with brain metastases that underwent SRS between October 2012 and August 2014 was performed. These patients had in total 116 brain metastases ranging in volume from

0.13 to 19.94 (mean: $3.82 \pm 4.02 \text{ cm}^3$). The prescribed dose average to the planning target volume (PTV) was $19.80 \pm 2.17 \text{ Gy}$ (range: 12-24 Gy).

4.2.2 | Treatment technique and treatment planning

Radiosurgery treatment of brain metastases at IPOCFG is linear accelerator (LINAC)-based. The LINAC is a Siemens Oncor Avant Garde equipped with a tertiary collimator, a BrainLAB mMLC of 3 mm minimum leaf width. The irradiation technique is based on 6 or 7 dynamic conformal arcs, almost always with a single isocenter per lesion where the mMLC leaves adapt to the lesion geometry according to the beam's eye view and so, further improve the conformity and homogeneity of the dose distribution.

Treatment planning is conducted using computed tomography (CT) and contrast-enhanced magnetic resonance (MR) images obtained using a T1 SE (spin-echo) sequence with Gadolinium contrast agent with no gantry tilt and a 1.0 mm thickness slices, fusion to assist structure delineation and the iPlan RT Dose treatment planning system, version 4.5 from BrainLAB [5].

4.2.3 | Brain mapping

Usually, the whole brain is divided in the main brain lobes shown in Figure 4.1.

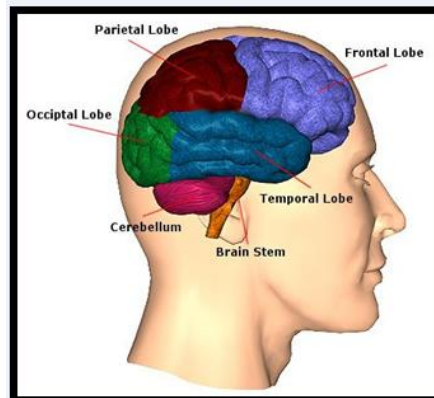


Figure 4.1 – Brain lobes. *From* [6].

Based on this division, axial, coronal and sagittal slices of the brain CT images were analysed and divided in some broad regions. Sagittal slices were divided in frontal, temporal, parietal, occipital and cerebellar lobes; coronal slices were divided in superior, inferior and central regions and axial slices were divided in anterior, posterior as well as in right, left and central sides – Table 4.1.

Table 4.1 – Regions defined in each brain plane.

SAGITTAL	CORONAL	AXIAL	AXIAL
Frontal	Central	Anterior	Right
Temporal	Superior	Posterior	Left
Parietal	Inferior	Central	Central
Occipital			
Cerebellar			

Figure 4.2 presents the pre-defined plain brain mapping, in each view. In Figure 4.2 a) the considered frontal, parietal, temporal, occipital and cerebellar lobes are shown. Figure 4.2 b) shows the superior, inferior and central regions while Figure 4.2 c) shows the anterior, posterior and central considered regions.

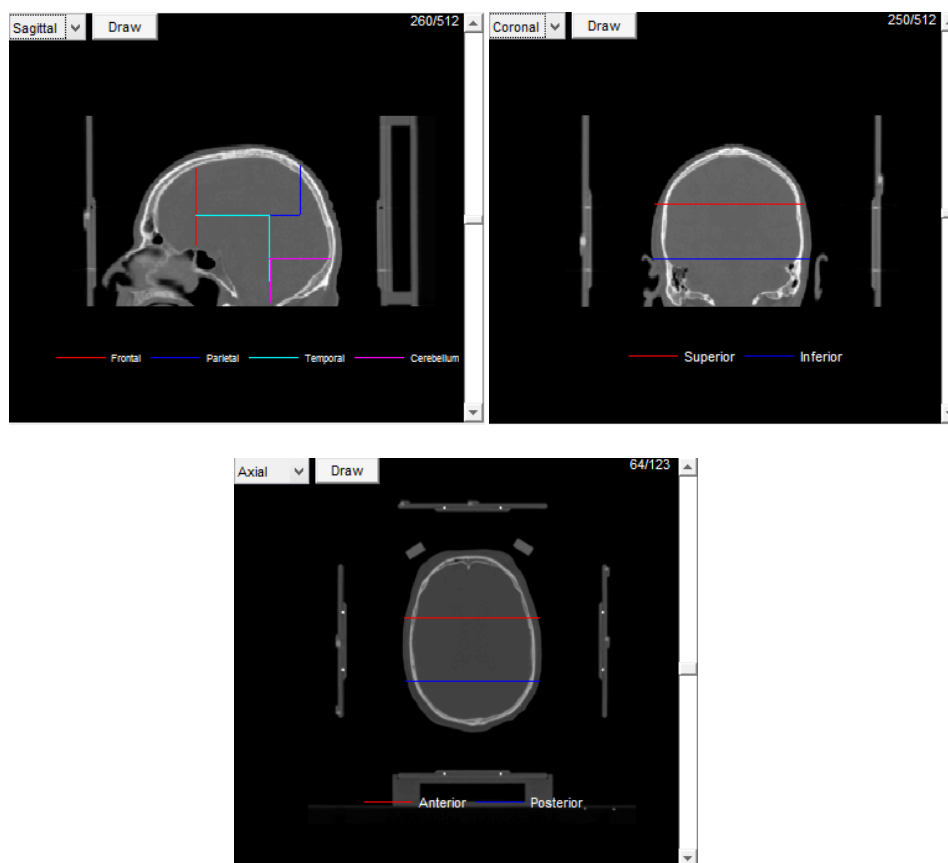


Figure 4.2 a), b) and c) – Sagittal, coronal and axial views.

Each brain metastases was assigned to a location referring to its position in coronal, sagittal and axial slices and grouped accordingly.

4.2.4 | Specific template creation

Through the retrospective analysis of the approved treatment plans for patients with brain metastases, a specific template was created for each geographic localization/brain region defined. In total, 13 right and 2 central specific templates have been created. The left templates were defined as precisely the mirrored of right specific templates.

Due to the high number of specific templates created, the quick selection of the most appropriate for each clinical situation could be an awkward task. So, a user-friendly graphical interface was developed using MATLAB version R2014a – Figure 4.3. The user just needs to point to the approximate position of the centre of the lesion in a coronal, sagittal or axial slice. After pointing to the lesion's centre in a slice of a specific view, the three coordinates are automatically defined so, it is possible to completely characterize the geographic localization and to see the projection of the chosen point in the other slice views.

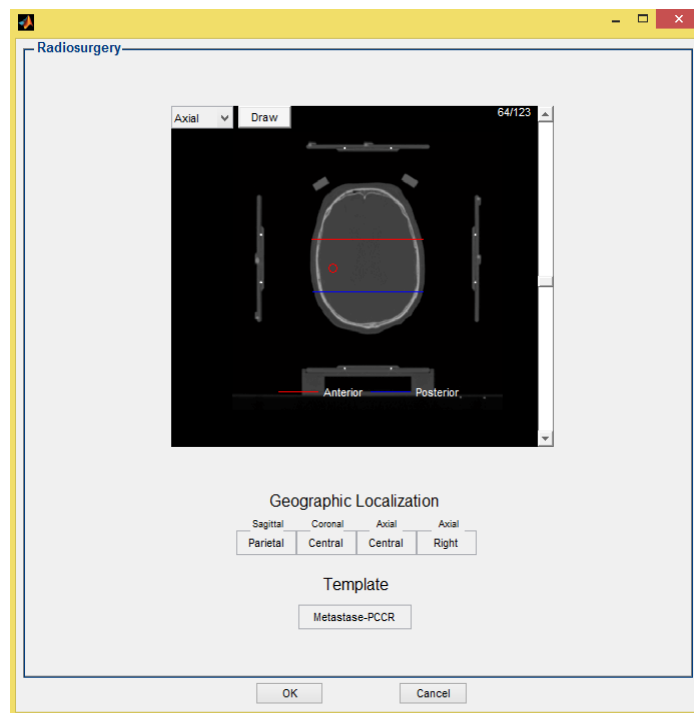


Figure 4.3 – User interface overview.

The specific template designation corresponds to 'Metastase-' plus the four initials of the geographic localization.

As referred, 15 templates with specific parameters for each location have been created and their acronyms are presented in Table 4.2.

Table 4.2 – List of treatment templates created grouped by brain lobe location.

Frontal	Parietal	Temporal	Occipital	Cerebellar
FSAR/L	PSPR/L	TICR/L	OCPR/L	CIPR/L
FCAR/L	PSCR/L	TCCR/L	OSPR/L	CICR/L
	PCCR/L	TCAR/L	OCCR/L	

Parietal specific templates were defined with 7 dynamic arcs while temporal, occipital, frontal and cerebellar specific templates have 6 arcs. The left templates were defined with mirrored values of corresponding right templates for table and collimator positions, gantry start and gantry stop.

Prescription details of all created specific templates are the same. The prescription defines the tumour plus 1 mm margin as a PTV and PTV's dose-volume constraints impose that 97.6% of the volume must receive the prescription dose and that the maximum dose must be less than 107% of the prescribed dose.

A comparison between the specific template created for each lesion localization and the generic template was made to demonstrate the advantages in terms of plan quality of using the specific template instead of the generic template and so, validate its development. The templates were independently applied and the direct plan quality provided by each one was assessed with no adjustments made for the mMLC shape.

To improve the conformity between the target volume and the prescription isodose and so sparing healthy tissues and protecting the critical organs (for some brain metastases locations), manual adjustments still had to be made in the mMLC shape. In the generic template these adjustments were made in all the arcs which is a very time consuming task. For speeding up the radiosurgery treatment planning, after the specific template application, the mMLC leaves were adjusted just in those arcs with higher dose weights.

4.2.5 | Treatment plan evaluation

The treatment plan quality evaluation is accomplished through the calculation of dose-volume indices, the visual inspection of the dose distribution image by image and the analysis of the dose-volume-histograms (DVH) for the different structures, namely the minimum dose in the PTV, the maximum dose in the critical organs and the volume of the critical organs that receives more than their tolerance dose.

The dose-volume indices assess the homogeneity of the dose distribution – MDPD (ratio between maximum dose and the prescribed dose) [7] – the coverage of

the target by the prescription isodose surface – TC (target coverage) [8] – and the conformity of the prescription isodose to the target volume – PITV (ratio of the prescription isodose surface volume to the target volume) [7] and COIN (conformity index) [9]. They have been reviewed in a former paper [10]. Calculated dose-volume indices must meet the criteria shown in Table 4.3 for a treatment plan to be acceptable.

Table 4.3 – Plan quality acceptability criteria.

Parameter	Value
TC	$\geq 95\%$
COIN	≥ 0.6
PITV	$\geq 1 \ \& \ \leq 2$
MDPD	$\geq 1 \ \& \ \leq 2$

4.3 | Results and Discussion

As previously referred the generic template is defined with six dynamic arcs with no specific adjustments for lesion location. The properties of this template, namely gantry start, stop and collimator positions are very conservative to ensure that there are no collisions during the treatment delivery but for specific templates properties are different according to the lesion location. As a large number of specific templates was developed, just an example is presented to outline the specificities. Table 4.4 shows the properties of the right generic template in black and the properties of the specific template named “Metastase-OCPR” in blue (OCPR = Occipital Central Posterior Right).

Table 4.4 – Properties of the six dynamic conformal arcs for the right generic template and the specific template “Metastase-OCPR”.

Arc	Table	Gantry Start	Gantry Stop	Collimator	Weighting (%)	Margin (mm)
1	10-10	230-220	350-350	320-350	18.6-18.6	3.0-3.0
2	37-37	220-210	340-340	320-310	16.5-16.5	3.0-3.0
3	64-64	210-200	340-340	300-300	13.4-13.4	3.0-3.0
4	90-90	200-200	340-340	270-270	10.3-10.3	3.0-3.0
5	300-300	150-160	20-20	60-30	19.6-19.6	3.0-3.0
6	335-335	140-150	10-10	45-30	21.6-21.6	3.0-3.0

Table positions and margin from mMLC to the PTV are the same for both templates and also for all specific templates. Arcs weighting in this case are also equal. The main difference is in gantry start positions that correspond to a larger arc amplitude for the OCPR template which improves the conformity of the dose distribution. Collimator angle changes are connected with gantry start angle changes to avoid collisions.

These differences are reflected in the treatment plan quality achieved with the application of each plan template. Table 4.5 presents the dose-volume indices obtained after the application of the generic template (right or left) and the specific template OCP (right or left) for lesions located at Occipital Central Posterior region (right or left side).

Table 4.5 – Dose-volume indices for the generic template and the template “Metastase OCP” application.

	TC	MDPD	COIN	PITV
Generic Template	0.978±0.011	1.083±0.024	0.576±0.061	1.682±0.218
Specific template OCP	0.979±0.010	1.081±0.024	0.581±0.059	1.671±0.211

The target coverage (TC) and the minimum dose in PTV are similar for both but COIN and PITV indices average values reflect that the specific template provides a better conformity than the generic template, on average. Dose distribution homogeneity is also better for the specific template. TC, MDPD and PITV all comply with the plan acceptability criteria. The COIN value for the treatment plans obtained with the template OCP is on average quite close to the minimum acceptable conformity value of 0.6 with the direct application of the specific template.

Due to the high number of specific templates developed (15), 13 groups were created to simplify the results assessment. Each group contains right, left and central templates, in other words, each group is identified by the first three locations, for example, “Metastase-OCPR” and “Metastase-OCPL” belong to the same group “Metastase-OCP”.

To summarize the comparison between generic and specific templates, the average values of the dose-volume quality indices were calculated for the generic template and all specific templates and presented in Table 4.6.

Table 4.6 – Dose-volume indices for generic template and specific templates.

	TC	MDPD	COIN	PITV
Generic Template	0.978±0.003	1.086±0.026	0.561±0.040	1.725±0.129
Specific template	0.978±0.004	1.080±0.016	0.564±0.039	1.716±0.132

In Table 4.6, PITV and COIN values indicate that specific templates provide a slightly better conformity than generic template. Target coverage is similar for both cases. The main difference is revealed by MDPD values. Homogeneity of the dose distribution is better for the specific template.

After the specific template application the mMLC leaves have been adjusted for the heaviest arcs.

Table 4.7 – Average dose-volume indices values for clinical cases of brain metastases, applying specific templates and with further adjustments in 1, 2, 3 and 4 arcs.

	TC	MDPD	PITV	COIN
Specific template	0.978±0.004	1.080±0.016	1.716±0.132	0.564±0.039
+ adj. in 1 Arc	0.978±0.003	1.079±0.016	1.609±0.101	0.599±0.034
+ adj. in 2 Arcs	0.979±0.003	1.078±0.016	1.523±0.087	0.633±0.033
+ adj. in 3 Arcs	0.978±0.004	1.073±0.012	1.436±0.069	0.670±0.029
+ adj. in 4 Arcs	0.977±0.004	1.071±0.012	1.404±0.060	0.684±0.025

Table 4.7 presents the dose-volume indices calculated for all studied clinical cases. Through a brief analysis we can see that on average, just the direct application of the specific template yields a poor conformity as for the corresponding average COIN. However, coverage and homogeneity already comply with the local acceptability criteria.

The manual adjustment of the mMLC shape contributes for improving the conformity. The mMLC adjustments in 1 arc allows an increase of the conformity but COIN values, on average, still do not comply with the plan acceptability criteria. Adjustments in 2 arcs decrease PITV in 11%, on average, and improves on average in 12% the COIN, leading to COIN values that on average comply with the plan acceptability criteria. With adjustments in 3 arcs COIN increases on average 19% and PITV decreases on average 16%. When 4 arcs are adjusted COIN values increase 21% and the PITV decrease 18%.

The homogeneity of the dose distribution is improved by the mMLC adjustments. The target coverage is not significantly affected and can even slightly

decrease with it, which is a consequence of the adjustment process decreasing the margin from the mMLC and the PTV for given incidences.

Results presented show a strong evidence that correction of the mMLC shape in three arcs leads to acceptable treatment plans. Figure 4.4 presents the dose-volume indices for the specific template group (each point represents the average value of one group) plus adjustment of the mMLC in three arcs – named Optimized Plans – versus the same indices for the corresponding Approved Plans with corrections in all arcs.

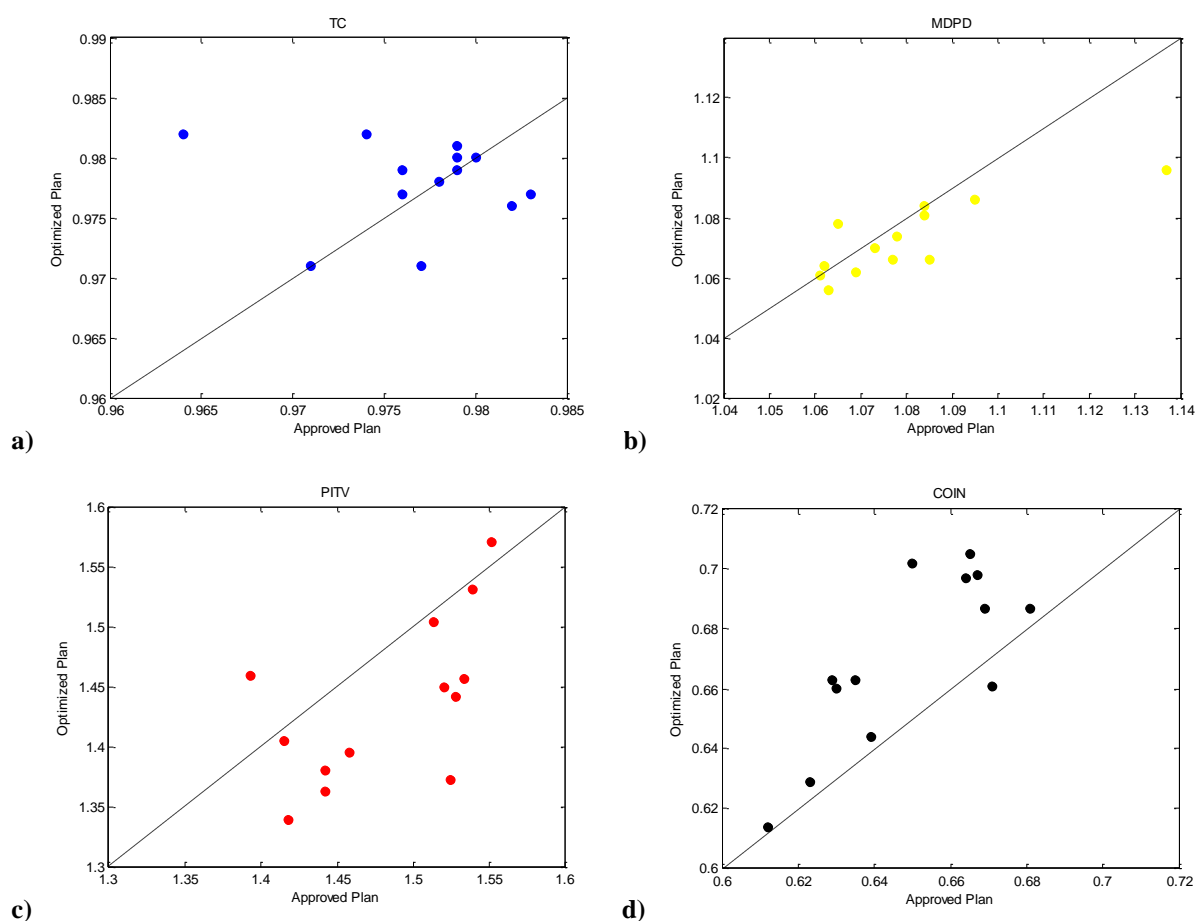


Figure 4.4 a), b), c), d) – TC, MDPD, PITV and COIN of the Optimized Plans for each metastases location group vs Approved Plans.

Equivalent results for both plans are represented by dashed lines that have a slope equal to 1. For Figure 4.4 a) and d) (TC and COIN), points above the dashed line represent specific templates groups whose Optimized plan is better than the corresponding Approved Plan. For Figure 4.4 b) and c) points above the dashed line represent specific templates groups whose Optimized Plan could not achieve the quality of the corresponding Approved Plan.

Figure 4.4 a), b), c) and d) confirm that the correction of the mMLC shape in just 3 arcs produce treatment plans that are better or equivalent to the approved treatment plans. In 10/13 groups the target coverage (TC) of the Optimized plan is equal or greater than the target coverage of the Approved plan and always greater than 95% (the minimum acceptable value). In 12/13 groups COIN is greater than COIN of the Approved plans and PITV of the Optimized plans is less than the PITV of the Approved plans in 11/13 groups. MDPD and PITV are always less than 2.0 and COIN always greater than 0.6, therefore plans are on average acceptable according to these indices.

As Table 4.7 demonstrates, the correction of just three arcs leads, on average, to treatment plans that comply with the treatment plan protocol.

Applying the specific templates OCP, OSP, CIP, TIC and TCC, treatment plan quality with manual adjustment of the mMLC leaves for just two arcs is similar or better than the Approved Plans quality.

When brain metastases are located near the brainstem or near other organ at risk, the dose constraint must be considered and therefore, the correction of just two or three arcs may not be enough. Normally the prescribed dose is greater than the organs at risk tolerance dose and target coverage and conformity are penalized for their sparing. Organs at risk prescription details were not included in any specific template group due to the high diversity of clinical cases.

To summarize the comparison between Approved and Optimized Plans, the average values of the dose-volume quality indices were calculated and are presented in Table 4.8.

Table 4.8 – Average values of the dose-volume quality indices for Approved treatment Plans and Optimized treatment Plans.

Parameter	Approved Treatment Plan	Optimized Treatment Plan
TC	0.977±0.005	0.978±0.004
MDPD	1.079±0.020	1.073±0.012
PITV	1.483±0.056	1.436±0.069
COIN	0.649±0.022	0.670±0.029

On average, for similar coverage, Optimized Plans are more conformal and homogeneous.

4.4 | Conclusions

In a retrospective treatment plan analysis of patients treated from October 2012 to August 2014 specific templates were created for each lesion location in the brain. A comparison between the plan quality of specific templates and that of the generic template standardly used at IPOCFG in the treatment planning of brain metastases was made. The direct application of specific templates allows on average better conformity and dose homogeneity. These represent a great advantage in terms of improving and speeding up the radiosurgery treatment planning phase.

To improve the conformity between the target volume and the prescription isodose and so sparing healthy tissues and protecting the critical organs (for some brain metastases locations), manual adjustments still have to be made in the mMLC shape. The specific template application with further adjustment in just three arcs allows obtaining a treatment plan quality that comply the local plan acceptability criteria and in most cases with better conformity, homogeneity and coverage than the approved plans where the mMLC had been adjusted in all arcs. This optimization reduces to around 1/2-1/3 the treatment planning time and so, the speeding up of the radiosurgery treatment planning was fully accomplished.

Furthermore, a useful graphical tool was developed to help the quick choice of the appropriate template to be used in each clinical case.

4.5 | References

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Stereotactic Radiosurgery of Brain Metastases: Analysis of Outcome

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Abstract

Purpose: To report the casuistic of all brain metastases treated with linear accelerator based stereotactic radiosurgery (SRS) at IPOCFG and to evaluate the outcome of SRS, identifying the factors that affect overall survival and local control.

Methods and Materials: One hundred sixty eight patients with 250 brain metastases underwent SRS between March 2008 and December 2014. Treated lesions ranged in volume between 0.13 and 21.63 cm³ (mean: 3.37 ± 3.56 cm³) and the median prescribed dose was 20 Gy (range 12 – 24 Gy). The more frequent primary tumour sites were lung (43.0%), breast (24.4%) and melanoma (7.6%). Overall survival and local control were estimated using the Kaplan-Meier method calculated from the time of SRS. A multivariate Cox proportional hazards model was used to determine the prognostic factors for treatment outcome (overall survival and tumour local control).

Results: The overall median survival after radiosurgery was 9 months. The 6 months, 1 and 2 years survival rates were 62%, 39% and 22% respectively. Age and primary tumour location were identified as important factors affecting overall survival. The median time to progression of metastases was 10 months (range: 3-19 months) and local control was achieved in 85.2% of the evaluated brain metastases. The 6 months, 1 year and 2 years local control rates were 97%, 81% and 73%, respectively and no significant prognostic factors were associated with local progression.

Conclusion: Stereotactic radiosurgery is an effective treatment for extending the survival of patients with brain metastases promoting high rates of tumour control in selected patients. Overall survival and local control reported results are in accordance with other published studies.

5.1 | Introduction

Brain metastases are the most common form of brain cancer and represent a significant cause of morbidity and mortality among cancer patients. According to the American Society for Radiation Oncology, brain metastases develop in 20-40% of cancer patients that have, predominantly, a primary tumour located in lung, breast, skin, kidney or colon-rectum [1].

Clinical manifestations can include focal neurological deficits depending on the lesion location, seizures, raised intracranial pressure, impairment in cognition and in functional status. Nowadays, with the growing use of magnetic resonance imaging more cases are being detected while still asymptomatic [2].

Historically, the life expectancy of patients with brain metastases is poor, but the outcome is more favourable in younger patients (less than 65 years old), with a single, small and asynchronous brain metastases, a controlled primary tumour, a Karnofsky performance status (KPS) ≥ 70 and without systemic metastases [2].

Current treatment options include neurosurgical resection, whole-brain radiation therapy (WBRT), stereotactic radiosurgery, chemotherapy or some combination of these. The choice of one modality over the others depends on the presence of multiple factors related to patients (age, performance status), tumour characteristics (number and size of the metastases, tumour type, extracranial disease activity), clinical situation and available treatment options [2,3].

Conventional WBRT is still frequently applied as a standard therapy for treatment of patients with brain metastases, namely for multiple brain metastases and patients with disseminated disease with poor prognosis. Side effects due to toxicity to the normal volume of the brain and lack of sustained local efficacy make this irradiation technique not the first option in patients with good systemic prognosis. Stereotactic radiosurgery (Gamma Knife or linear accelerator-based) has become a current treatment for those patients that have lesions smaller than 3-4 cm in diameter. It has been demonstrated in several randomized trials that stereotactic radiosurgery (SRS) accomplishes highly effective and predictable local control for single and multiple brain metastases, even for conventionally radioresistant metastases from melanoma or renal cancer [4-6]. Moreover, on neuroimaging, brain metastatic lesions usually appear fairly spherical and well-defined, therefore they are a suitable target for SRS treatment.

Remote brain metastases are reported in 33-42% after WBRT [7,8] and in 39-52% after radiosurgery [9-11]. Radiosurgery can be used repeatedly for remote recurrences or new metastases after WBRT, while WBRT is generally applied only once.

Brain metastases smaller than 3-4 cm in diameter represent an ideal target for SRS due to the spherical shape, distinct radiographic and pathologic margins and their tendency to displace rather than invade adjacent brain tissue. SRS allows the treatment of brain metastases in almost any location, including eloquent or deep regions that could be difficult or impossible to access surgically. The main disadvantages of radiosurgery are its inability to quickly address the symptoms caused by the mass effect, limited application for lesions larger than 3-4 cm in diameter and metastatic lesions located in or near structures with low tolerance to radiation such as optic nerves, chiasm or brainstem and possible functional changes [12]. SRS is not recommended in brain metastases larger than 3-4 cm in diameter due to the increased risk of a later edema development and normal brain tissue damage. In these cases, surgical resection should be considered in patients with controlled systemic disease and with metastases in an accessible location [2]. Hypofractionated radiosurgery delivered in 3-5 fractions over multiple days is another alternative therapeutic option [13]. Patients with brain metastases that cause compression of neuronal functional structures or intracranial hypertension may undergo surgery in order to achieve better outcome [2].

The purpose of this work was to report the casuistic of all brain metastases treated at IPOCFG with linear accelerator (LINAC)-based radiosurgery from March 2008 to December 2014 and evaluate the treatment outcome, identifying the factors that may influence overall survival and local control.

5.2 | Methods and Materials

5.2.1 | Lesion characteristics and SRS procedures

One hundred and sixty eight patients (87 females and 81 males) with 250 metastases underwent SRS between March 2008 and December 2014. In 108 patients only one metastase was treated (64.3%), in 43 patients two metastases were treated (25.6%), three lesions were treated in 13 patients (7.7%) and four or more lesions were treated in 4 patients (2.4%).

Lesions characteristics are listed in Table 5.1. The patients average age at the time of SRS was 60 years old (range 22-89 y) and the most common primary tumour sites were lung (43.0%), breast (24.4%) and melanoma (7.6%). The other group of primary tumours includes ovary, prostate, kidney, thyroid and colon-rectum locations, for example. The most common locations in the brain were parietal lobe (36%) followed by temporal (19.2%) and occipital lobe (19.2%).

The mean planning target volume (PTV) was $3.37 \pm 3.56 \text{ cm}^3$ (range 0.13 – 21.63 cm^3) and the median prescribed dose was 20 Gy (range 12 – 24 Gy). The average values of the dose-volume indices were: 0.98 ± 0.03 for the coverage index, 1.08 ± 0.04 for the homogeneity index and 0.64 ± 0.07 for the conformity index.

Table 5.1 – Summary of lesion characteristics and dose-volume indices.

Parameter	Value
Number of patients	168
Number of treated lesions	250
Mean age (range)	60 (22-89)
Sex(F/M)	87/81
Number of treated lesions per patient	
1 lesion	108 (64.3%)
2 lesions	43 (25.6%)
3 lesions	13 (7.7%)
4 lesions	3 (1.8%)
more than 4 lesions	1 (0.6%)
Primary tumour location	
Lung	74 (43.0%)
Breast	42 (24.4%)
Skin	13 (7.6%)
Others	43 (26%)
Lesions location	
frontal	24 (9.6%)
parietal	90 (36.0%)
temporal	48 (19.2%)
occipital	48 (19.2%)
cerebellar	40 (16.0%)
Treated volume (cm^3)	
Mean (range)	3.37 (0.13-21.63)
Mean prescribed dose (Gy)	19.33 ± 2.23
Mean TC ¹ (%)	0.98 ± 0.03
Mean MDPD ²	1.08 ± 0.04
Mean COIN ³	0.64 ± 0.07

¹ TC= Target Coverage [14]

²MDPD= Maximum Dose to Prescribed Dose [15]

³COIN= Conformity Index [16]

Each patient was immobilised with the Brainlab Stereotactic Headring and underwent 1.5 mm slice thickness computed tomography (CT) scans (with and without contrast) on a dedicated big-bore CT simulator (Siemens Sensation Open) with the

Brainlab CT Localizer. High-resolution 3D T1 weighted single dose gadolinium contrast (0.1 mmol/kg) 1.5T magnetic resonance (MR) images of the whole brain were also obtained for all patients, usually within a week of planned treatment. Both CT and MR images were electronically transferred to the therapy planning system (iPlan RT Dose v4.5, BrainLAB) for co-registration. All fusions were visually inspected and approved by the neuroradiologist. The PTV corresponded to the delineated target volume plus a 1 mm isotropic margin.

Treatment plans were computed using a pencil beam algorithm for a 6 MV photon beam energy. A dose resolution of 1 mm was set. The adaptive grid option was used for the calculation of the dose matrix. In this option the dose grid size is automatically adapted to the volume of small structures and so guarantees at least 10 voxels are always used for dose computation in all directions. SRS was performed using the micro-multileaf collimator (mMLC) of Brainlab, with full advanced integration in a Siemens Oncor Avant-Garde linear accelerator using the 6MV photon mode.

Clinical records of these patients including basic information (ID, gender, year of birth, primary tumour and date of death (when it occurred)), treatment and quality control (date, treatment duration, dosimetric parameters) and follow-up details (number of imagiologic controls, number and date of follow-up clinical appointments) were stored in a dedicated database. This database was developed in-house using MySQL Workbench Visual Database Designer version 3.2 CE.

5.2.2 | Follow-up and outcomes analysis

The median clinical follow-up after radiosurgery was 7 months for the considered range of 1-24 months. Despite the maximum follow-up time of our series being 69 months, eighteen patients with longer follow-up time have been censored at 24 months to prevent degradation of the statistical power of the study. Patients were examined clinically one month after radiosurgical treatment and then every 2/3 months or as appropriate according to the neurologic conditions. Imagiologic control (MR/CT) was done every 3/4 months or also as appropriate according to the neurologic conditions.

Lesion's diameters were measured in two dimensions and in every image control set in order to assess the outcome of the treatment. Response to radiosurgery was not evaluated in 88 metastatic lesions due to patient's death before the date for the first imagiologic control, insufficient data or very recent treatment. Therefore, 162

metastases were eligible for local control analysis. Tumour response was classified according to Macdonald 2D criteria [17]. MacDonald's criteria proposed four categories to treatment outcome: complete response (CR), a complete disappearance of tumour; partial response (PR), at least 50% decrease in tumour size; progressive disease (PD), at least 25% increase in tumour size and stable disease (SD) neither PR nor PD.

5.2.3 | Statistical analysis

Overall survival and tumour local control of the patients that underwent SRS were estimated using the Kaplan-Meier method calculated from the time of SRS. The following factors were tested in order to assess their influence in overall survival: age (< 65y and \geq 65y), number of treated brain metastases (1 vs >1) and primary tumour sites (breast vs lung vs other). Metastases location, metastases volume, primary tumour location and patient's age were tested in order to assess their influence in local control.

Comparisons between groups were performed using the log-rank test. A multivariate Cox proportional hazards model was used to determine the prognostic factors for treatment outcome (overall survival and local control). Factors found significant in the crude model were included in the final model. A probability value \leq 0.05 was considered statistically significant.

Statistical analysis was performed using R version 3.1.2 software.

5.3 | Results

5.3.1 | Overall Survival

Median overall survival for the entire group was 9 months (95% Confidence Interval (CI) 8-12 months) from the date of their first radiosurgery. The 6 months, 1 year and 2 years survival rates were 62%, 39% and 22%, respectively – Figure 5.1.

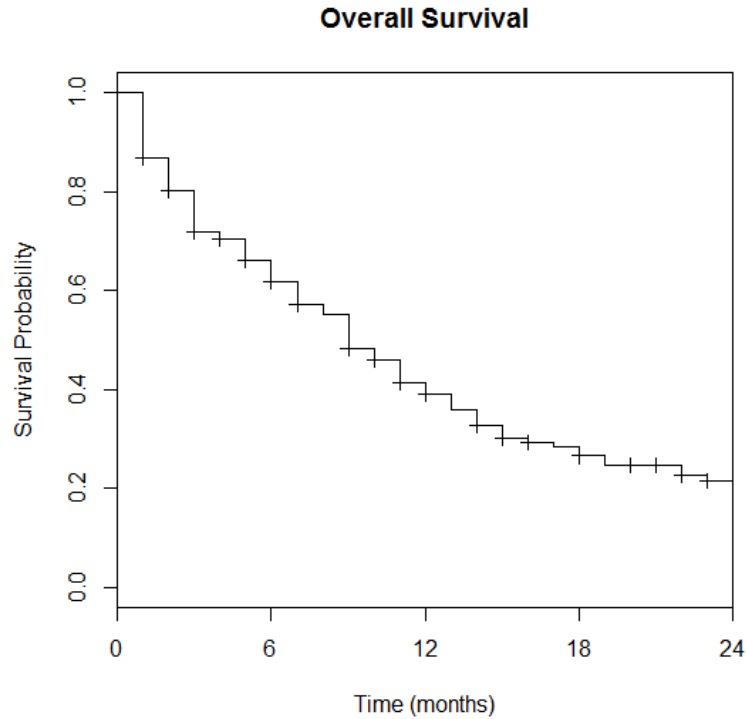


Figure 5.1 – Kaplan-Meier analysis of overall survival.

Univariate analysis showed that age and primary tumour location were significant predictive factors for survival ($p < 0.05$) – Table 5.2.

Table 5.2 – Univariate survival and multivariate survival analysis.

Variable	No of patients	Survival time Median (months)	Univariate Analysis	Multivariate Analysis
			Hazard Ratio (95 % CI)	Hazard Ratio (95 % CI)
Age (years)				
< 65	104	12	0.63 (0.42-0.93)	–
≥ 65	64	7	1	–
No of brain metastases				
1	109	9	0.88 (0.60-1.29)	–
>1	59	12	1	–
Primary Tumour				
Breast cancer	42	13	1	1
Lung cancer	74	9	1.40 (0.86-2.28)	1.30 (0.79-2.13)
Others	52	6	1.80 (1.07-3.01)	1.77 (1.06-2.97)

Cox proportional hazards regression indicates that the risk of patients with less than 65 years old to die earlier after SRS is lower than the risk associated to patients with an age greater than 65 years old (hazard ratio = 0.63, 95% confidence interval = 0.42 to 0.93, $p=0.020$).

Median survival time for patients with breast cancer that underwent SRS was 13 months, for patients with lung cancer was 9 months and for patients with other cancer was 6 months. Cox model points to a statistically significant difference in overall survival between Breast cancer and Other cancer groups (hazard risk = 1.80, 95% confidence interval = 1.07 to 3.01, $p=0.026$). Figure 5.2 shows a comparison of overall survival for the different primary tumour groups (breast cancer, lung cancer and other).

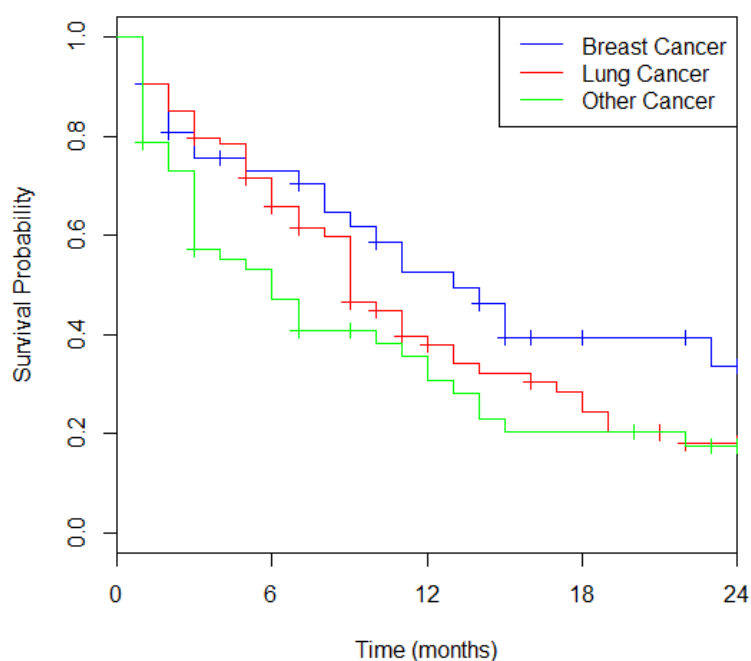


Figure 5.2 – Comparison of different primary tumour locations with respect to survival.

Age and primary tumour location were included in a multivariate analysis of outcome performed using a Cox proportional hazards regression model.

In the multivariate analysis primary tumour and age proved to be significant variables ($p<0.05$). Cox model demonstrates that regardless of age, there remains a statistically significant difference in overall survival between Breast cancer and Other cancer groups (hazard ratio = 1.77, 95% confidence interval = 1.06 to 2.97, $p=0.030$).

5.3.2 | Local Control

One hundred sixty two metastases were eligible for local control analysis. Local control was achieved in 85.2% of the evaluated brain metastases and the median time to lesion progression was 10 months (range: 3-19 months). Applying Macdonald's criteria to our metastases series, a complete response (CR) was noted in 18 metastases (11.1%), partial response (PR) in 11 metastases (6.8%), a stable disease (SD) in 109 metastases (67.3%) and a progressive disease (PD) in 24 brain metastases (14.8%).

Figure 5.3 shows the local control curve.

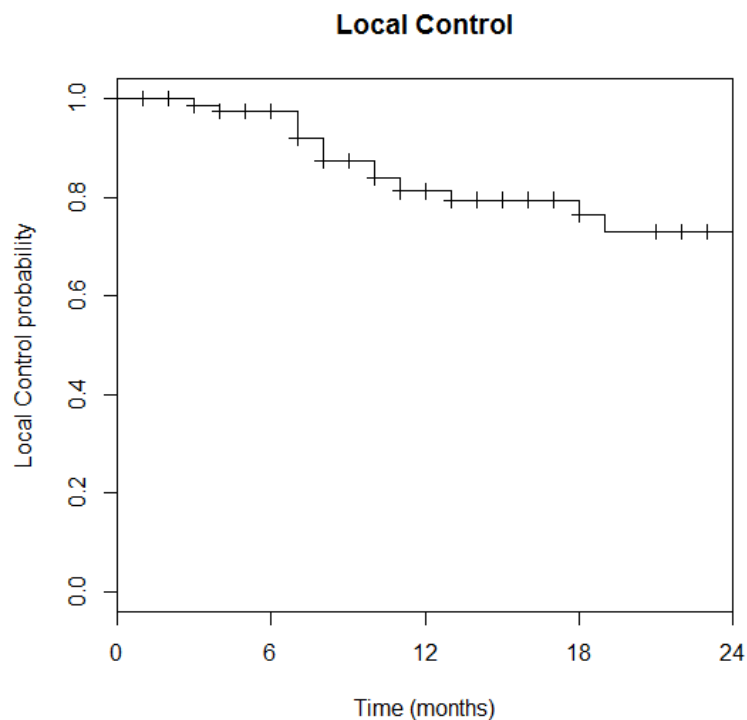


Figure 5.3 – Kaplan-Meier analysis of local control.

The 6, 12 and 24 months actuarial rates without local failure after SRS were 97%, 81% and 73%, respectively.

In univariate analysis, metastases location, metastases volume, primary tumour location and patient's age were not significantly correlated with local control rate.

5.4 | Discussion

In the present study we have evaluated the clinical outcome in 168 consecutive patients treated with SRS from March 2008 till December 2014, with 250 brain metastases. Median overall survival for the entire group was 9 months (95%

Confidence Interval 8-12 months) from the date of their first radiosurgery. The 6 months, 1 year and 2 year survival rates were 62%, 39% and 22%. These results are in accordance with previous studies that report median survival ranging from 6-14 months for brain metastases [8, 18-21].

Univariate analysis showed that age and primary tumour location were significant predictive factors for survival ($p < 0.05$) – Table 5.2. The number of brain metastases had not a significant impact on survival, similarly to some recent studies [21-23] and differently from earlier published series [24].

In univariate analysis, Cox proportional hazards regression indicates that the risk of patients with less than 65 years old to die earlier after SRS is lower than the risk associated to patients with an age greater than 65 years old (hazard ratio = 0.63, 95% confidence interval = 0.42 to 0.93, $p = 0.020$). Furthermore, Cox model points to a statistic significant difference in overall survival between Breast cancer and Other cancer groups (hazard risk = 1.80, 95% confidence interval = 1.07 to 3.01, $p = 0.026$) which means that from our data we just may conclude that breast cancer metastases have a larger survival rate than any other cancer type.

In multivariate analysis primary tumour and age proved to be significant variables ($p < 0.05$). In this case, Cox model allows to say that regardless of age, the risk of earlier death for patients with a primary tumour located in the lung is, on average, 30% (hazard ratio = 1.30, 95% confidence interval = 0.79 to 2.13, $p = 0.303$) greater than the same risk associated to patients with a primary tumour in the breast; the risk that a patient dies earlier when the primary tumour belongs to the Other cancer group is on average 77% (hazard ratio = 1.77, 95% confidence interval = 1.06 to 2.97, $p = 0.030$) greater than the risk associated to patients with a primary tumour in the breast. Finally, the risk associated to patients whose primary tumour belongs to the Other cancer group is on average 29% (hazard ratio = 1.29, 95% confidence interval = 0.85 to 1.95, $p = 0.231$) greater than in patients whose primary tumour is located in the lung. However just the difference between *Breast* and *Other* groups is statistically significant.

These results are in accordance with previous series of SRS for brain metastases that report a slightly higher prognostic for patients with a primary tumour located in the breast when compared to other groups of cancer patients [23,25-28].

Similarly to other reports on SRS, we used a definition of local progression proposed by Macdonald's, based on imagiologic control [20,29]. Local control was

achieved in 85.2% of the evaluated brain metastases and the median time to lesion progression was 10 months (range: 3-19 months). The 6, 12 and 24 months actuarial rates without local failure after SRS were 97%, 81% and 73%, respectively. Comparable outcomes were achieved in other SRS retrospective series. Molenaar et al. in an analysis of 86 patients with brain metastases that underwent SRS reported local control rates of the 82%, 63% and 57% at 6, 12 and 24 months respectively [20]. Similarly, Bernard et al. reported actuarial local control at 6 months and 12 months of 87% and 68% on a study of 54 patients with a total of 103 metastases treated with SRS [30].

No significant prognostic factors were associated with local control. Several groups have reported that higher prescription doses (prescribed dose greater than 18 Gy) and small tumour volume are associated with better tumour control [20, 31-34]. Some radiosurgery series also described primary tumour site correlation with local control. Reported rates were 90–94% for breast cancer metastases [35-38] and 81–98% for brain metastases of lung cancer [39, 40], 73–90% for melanoma [41,42] and 83–96% for renal cell cancer [40,43,44]. Garsa et al. [33] retrospectively analysed 228 patients with 401 brain metastases from non-small cell lung cancer and they found higher risk of local failure for cerebellar metastases. The same conclusions were reported by Sansur et al. [45] and Alexander et al. [34].

Although local control of the treated metastases could be essential for the neurologic integrity and quality of life, it may not have direct impact on patient's survival due to the influence of the characteristics and status of the systemic disease in patient's outcome [46-48].

5.5 | Conclusion

Overall survival, local control and factors that may influence treatment outcome were evaluated in 168 patients treated with SRS in 250 metastases between March 2008 and December 2014 at IPOCFG. Median overall survival was 9 months from the date of the SRS for a follow up time of 24 months. The 6 months, 1 year and 2 years survival rates were 62%, 39% and 22%, respectively. These results are in accordance with other published studies that report a median survival ranging from 6-14 months. Statistical analysis showed that age and primary tumour location were significant predictive

factors for survival, whereas the number of brain metastases was not shown to be a significant factor.

Local control was achieved in 85.2% of the evaluated brain metastases. The 6, 12 and 24 months actuarial rates without local progression after SRS were 97%, 81% and 73%, respectively. No significant factors were associated with the local tumour progression.

The reported outcome of SRS was comparable to previous studies. These results support the conclusions that SRS provides a high local control rate, improves the cumulative survival and may be associated to low normal tissue complication probability. Based on identified prognostic factors, the selection of eligible patients is an important concern to maximize radiosurgery benefits.

5.6 | References

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**Dosimetric comparison of multileaf
collimator systems for intracranial stereotactic
radiosurgery**

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Abstract

Purpose: At IPOCFG, stereotactic radiosurgery is performed using a micro-multileaf collimator (3mm minimum leaf width), mMLC m3, with full advanced integration in a linear accelerator. This work aimed to evaluate if the replacement of the standard 82-leaf multileaf collimator with 1cm leaf width, by a 160MLC (MLC-160) with 5mm leaf width, would allow to dispense the use of the m3 without compromising the treatment plans quality.

Methods and Materials: 67 metastases and 23 meningiomas formed the basis of this retrospective planning study. For each clinical case two treatment plans were generated: one using the m3 and the other using the MLC-160. The same irradiation technique, with multiple noncoplanar conformal arcs, was used and all arc parameters were kept the same. The dosimetric differences from both plans were quantified in terms of target coverage and dose conformity. Dose-volume histograms for the planning target volume (PTV) and the organs at risk (OARs) were also recorded and analysed. The Wilcoxon signed rank test was performed to evaluate statistical differences.

Results: The characteristics associated with the MLC-160 system (larger leaf width and static conformal arcs) contributed to a poorer dose conformity, mainly for irregular shaped or small lesions and for lesions at close proximity to OARs. Statistically significant differences were found in terms of the minimum dose for lesions $\leq 0.5 \text{ cm}^3$ and irregular lesions. As a consequence, almost 35% of the considered clinical plans would not be clinically acceptable if the intended replacement of the collimation system would take place.

Conclusion: The mMLC yields dosimetric benefits in radiosurgery. The treatment of lesions with complex shapes or at close proximity to OARs do benefit from the use of a fine leaf-width MLC.

6.1 | Introduction

Stereotactic Radiosurgery (SRS) is a treatment technique characterized by the administration of high doses of radiation in a single fraction with high accuracy to a small and well-defined intracranial target, while limiting the dose to surrounding normal tissues [1].

In the early development of linear accelerator (LINAC)-based systems, circular collimators of different diameters coupled to the LINAC were used and the SRS treatment was performed with multiple convergent and noncoplanar arcs [2,3]. Since then, LINAC-based SRS has become highly sophisticated. The introduction of the multileaf collimator (MLC) has incorporated new features to radiotherapy and also the SRS process, enabling the generation of irregular field shapes allowing improvements in conformity and homogeneity of the dose distribution [1].

The impact of the narrower leaf widths on radiotherapy treatment planning has been studied by many authors, but with mixed results [1-10]. Kubo et al. [7] were the first to analyse the impact of the MLC leaf width on stereotactic radiosurgery and 3D conformal radiotherapy treatment plans, using 1.7, 3 and 10 mm leaf width MLC systems. They showed that for radiosurgery treated lesions, the 1.7 and 3 mm leaf width allowed to comply the RTOG (Radiation Therapy Oncology Group) treatment planning guidelines for SRS, in most cases. On the other hand, Burmeister et al. [9], reported no apparent clinically advantage in the replacement of a 10 mm by a 5 mm MLC system on patients treated with intensity-modulated radiotherapy, except for very small target volumes or those with concavities that are small with respect to the MLC leaf width. More recently, Tanyi et al. [10] performed a dosimetric comparison between MLC systems with 2.5 mm and 5 mm leaf width for the SRS treatment of 68 intracranial lesions and demonstrated small dosimetric benefits of the 2.5mm leaf width MLC system over the 5mm leaf width system.

The present study aimed at justifying a management decision on the replacement of the standard 82-leaf Optifocus MLC collimator (1 cm leaf width at isocenter) installed in the Siemens Oncor Avant Garde linear accelerator presently used for SRS with a tertiary BrainLab mMLC (m3). We would like to evaluate if the replacement of the 82-leaf MLC by a 160 MLC with 5 mm leaf width at isocenter would enable to dispense the use of the m3 mMLC without significantly jeopardizing the quality of the treatment plans. This evaluation would include quantifying the amount

of the eventual losses in terms of plan quality and assessing the characteristics of the lesions that would mostly be affected by the eventual replacement.

6.2 | Methods and Materials

At IPOCFG SRS is performed since February 2008 using the micro-multileaf collimator mMLC of BrainLab (3 mm minimum leaf width) – m3, with full advanced integration in a Siemens Oncor Avant-Garde linear accelerator using the 6 MV photon mode. The treatment technique consists in 6-7 dynamic conformal arcs rotating about a single isocenter using the m3 to conform to the target volume every 10° incidence.

6.2.1 | Patients selection

For the proposed retrospective planning study, 67 metastatic brain lesions and 23 meningiomas treated with SRS between November 2008 and December 2014 have been selected. The clinical cases were categorised into four groups: (I) brain metastases with volume $\leq 0.5 \text{ cm}^3$ (n=36), (II) brain metastases with volume $> 0.5 \text{ cm}^3$ (n=16), (III) brain metastases located in close proximity to organs at risk (n=15) and (IV) meningiomas (n=23). Table 6.1 summarizes the group’s characteristics.

Table 6.1 – Summary of group’s characteristics.

Parameter	group I (Metastases)	group II (Metastases)	group III (Metastases)	group IV (Meningioma)
No. of lesions	36	16	15	23
Average Target Volume ($\pm 1\sigma$) (cm^3)	0.30 ± 0.12	3.40 ± 2.82	3.80 ± 3.18	3.90 ± 3.03
Organ(s) at risk	None	None	Brainstem	Brainstem, optical nerves, chiasm

The groups were created to represent the different clinical situations in our SRS experience. Groups I and II were intended to compare the volume effect, group III for critical organ sparing and group IV was chosen for shape effect assessment. As meningioma cases may appear in any brain location, including at close proximity to critical structures, some cases in group IV were also compared for critical organ sparing.

6.2.2 | Collimators

The m3 has 26 pairs of leaves: from centre to periphery 14 pairs with 3 mm width, six pairs with 4.5 mm and six pairs with 5.5 mm width. The maximum possible field size is $10 \times 10 \text{ cm}^2$ at isocenter. It is a tertiary or additional collimator which must be attached to the LINAC head every time a stereotactic treatment is to be delivered. The irradiation technique is based on dynamic conformal arcs using in almost all cases a single isocenter for each lesion. During irradiation, the gantry is rotating while the leaves of the mMLC move according to the beam's eye view (each leaf of the m3 moves linearly at 10° intervals interpolating from the initial position to the next calculated position) – Figure 6.1.

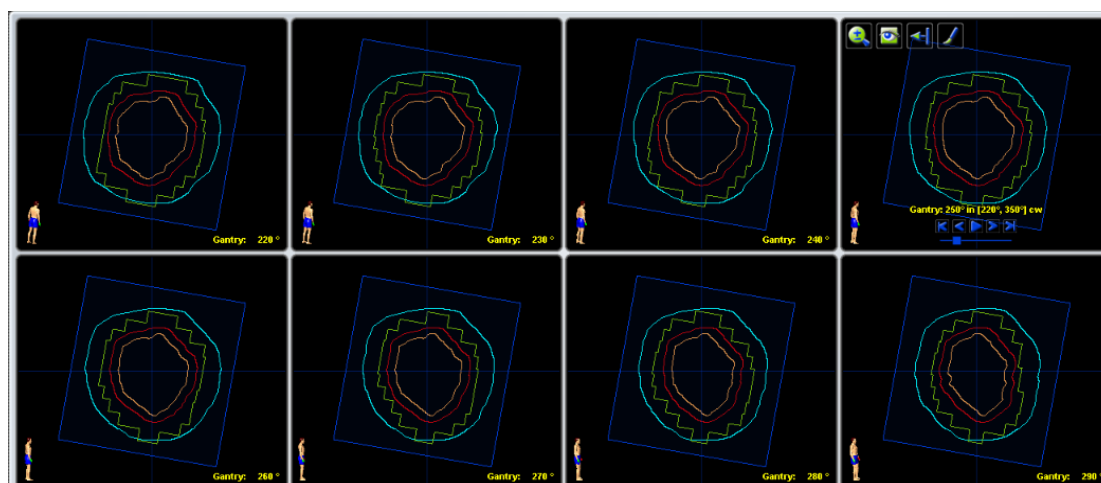


Figure 6.1 – Beam's eye view of single 130° dynamic arc for 3-mm micro-MLC (m3) showing the collimator leaves position for each 10° interval between 220° - 290° .

The Siemens 160 Multileaf Collimator has 160 leaves – 80 on each bank with a leaf width of 5 mm at isocenter over the full maximum field size of $40 \times 40 \text{ cm}^2$. It is integrated on the LINAC head replacing the X-jaws. The irradiation technique is based on static conformal arcs as the Oncor Avant-Garde linac does not include the dynamic irradiation mode. The radiation field is adjusted to the largest shape of the target lesion in just one incidence per arc. During irradiation, the gantry is rotating and the MLC shape remains static – Figure 6.2.

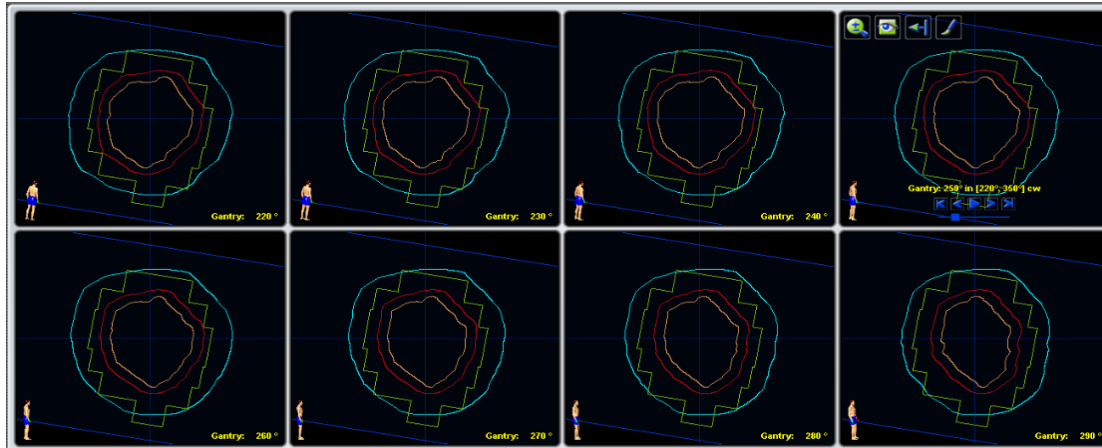


Figure 6.2 – Beam's eye view of single 130° static arc for 5-mm multileaf collimator (MLC-160) showing collimator leaves position for each 10° interval between 220°-290°.

6.2.3 | Machine Profiles Comparison

The current study is not just a simple comparison of different MLC leaf widths. It also includes the assessment of two dose delivery systems associated to each MLC.

The micro-multileaf collimator of BrainLab is the collimator system used at our institution for SRS treatments. The corresponding basic dosimetry was locally performed during the commissioning process and the dosimetric database was stored in the Physics Administration module (PAM) of the treatment planning system (iPlan, BrainLab). For the present study, BrainLab provided a full dosimetric database of an external linear accelerator of the same model (Oncor) equipped with a Siemens 160 Multileaf Collimator which was stored as a new Machine Profile in PAM.

Before starting the retrospective planning study, a dosimetric comparison between the basic dosimetry databases corresponding to the two delivery systems was performed to evaluate if the characteristics of the radiation field were comparable and to validate the external machine dosimetry. For the m3 the local nominal linac output for a 10×10 cm² field size with source surface distance of 100 cm and at a depth of 5 cm was 0.867 Gy/100 MU (monitor units). For the external MLC-160 system the nominal linac output was defined for a 10×10 cm² with source surface distance of 100 cm and at a depth of 10 cm as 0.677 Gy/100 MU. A renormalization of the nominal output for the MLC-160 to a depth of 5 cm was made and the obtained value of 0.872 Gy/100 MU differs from that of m3 in just 0.6%. The depth dose profiles were also compared for the common field sizes: 3×3 cm², 6×6 cm², 8×8 cm² and 10×10 cm². The obtained depth dose profiles coincided within less than 1%, with larger differences for smaller fields, mainly at the buildup region.

Figure 6.3 a) and b) presents the depth dose profiles obtained using field sizes of $3 \times 3 \text{ cm}^2$ and $8 \times 8 \text{ cm}^2$ for the m3 and MLC-160 collimator systems.

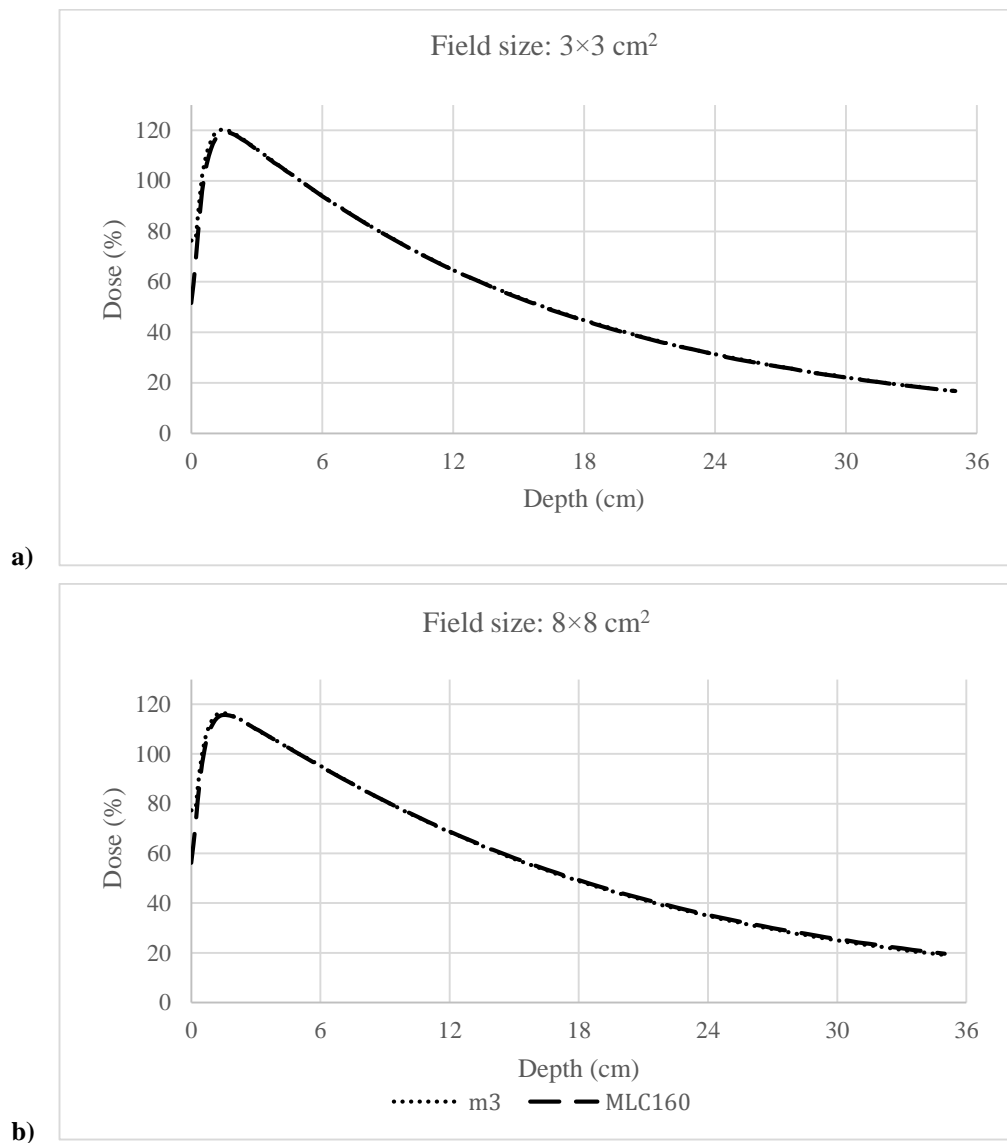


Figure 6.3 – Depth dose profiles of different field sizes for both collimator systems: a) $3 \times 3 \text{ cm}^2$; b) $8 \times 8 \text{ cm}^2$.

Based on the previous comparisons, we have assumed that the two dosimetric machines could be used for the proposed planning study.

6.2.4 | Treatment planning

Treatment planning is locally conducted using iPlan treatment planning system, version 4.5 from BrainLAB. Contrast enhanced magnetic resonance (MR) images of each patient are co-registered with planning computed tomography (CT) images

acquired in a big-bore CT simulator (Siemens Sensation Open). A head ring frame fixation system and the corresponding CT-localizer are used to enable the required stereotactic transformation performed at the planning workstation. The neuroradiologist approves the image fusion and delineates the gross tumour volume (GTV) and the relevant organs at risk (OARs) on the MR images. Subsequently, the planning target volume (PTV) is defined as the GTV plus an isotropic margin of 1mm incorporating the clinical target volume (CTV) and accounting for setup errors and other possible isocenter localizing uncertainties.

For the present study, reference plans were created for m3. The plans used for treatment have not been used to prevent planner skills dependence. All clinical cases were re-planned with both MLCs using exactly the same treatment planning parameters, such as the isocenter location, the number of noncoplanar conformal arcs, the MLC margin, the gantry start and stop angles, the collimator and table rotation angles for each arc, and the prescription dose.

Treatment plans were computed using a pencil beam algorithm for a 6 MV photon beam energy. A dose resolution of 1 mm was set. The adaptive grid option was used for the calculation of the dose matrix. In this option the dose grid size is automatically adapted to the volume of small structures guaranteeing at least 10 voxels for dose computation in all directions.

6.2.5 | Plan quality evaluation parameters

Target Coverage (TC) [11], Conformation Number (CN) [12], Conformity Index (CI) [11], Conformity/Gradient Index (CGI) [13] and the volume of normal tissue receiving at least 100% of the prescription dose (V_{NormPl}) were used to compare the treatment plans. The dose-volume indices have been reviewed in a former paper [14]. PTV dose-volume-histogram (DVH) parameters including minimum dose and maximum dose were computed and recorded. DVHs for the critical structures were compared in terms of the dose received by 0.1 cm³ of brainstem ($D_{0.1\text{cm}^3}$) as well as the volume of critical organ that receives more than its tolerance dose and more than the prescribed dose. [10].

a) Improvement ratio

A ratio to evaluate the improvement in each dose-volume index and the minimum and maximum dose to PTV between the two rival plans (a plan obtained with the m3 vs a plan obtained with the MLC-160) was defined as:

$$\text{Improvement ratio (IR) (\%)} = \frac{\text{Index}_{MLC-160} - \text{Index}_{m3}}{\text{Index}_{m3}} \times 100(\%) \quad 6.1$$

For the dose-volume indices and the minimum dose to PTV a positive improvement ratio means that MLC-160 would performed better than m3 in terms of the corresponding index. When the maximum dose to PTV is evaluated, a positive improvement ratio means that the MLC-160 would contribute to a more heterogeneous dose distribution, what means a lower performance of MLC-160 vs. m3.

6.2.6 | Statistical Analysis

Statistical analysis was carried out using MATLAB version R2014a. The Wilcoxon signed rank test for paired samples was performed to assess differences between plans, with a p-value < 0.05 defining statistical significance.

6.3 | Results

6.3.1 | PTV coverage, Dose conformity and Conformity/Gradient index

The dosimetric indices and their improvement ratios according to the MLC leaf width (MLC-160 vs. m3) for the four groups of clinical cases are summarized in Table 6.2. The Wilcoxon signed rank tests the null hypothesis which is that the median difference between pairs of observations is zero. Therefore, the p-value column in the table exhibits the probability of rejecting the null hypothesis (if $p < 0.05$ the indices are statistically different and the improvement ratio is real, either positive or negative). Also the median values of each evaluated parameter were included in Table 6.2.

Table 6.2 – Average quality indices and corresponding improvement ratios ($\pm 1\sigma$) of MLC-160 versus m3. Median values are shown in parenthesis.

Group	Index	m3	MLC-160	IR (%)	p-value
I (n=36)	TC	0.98 \pm 0.01 (0.98)	0.98 \pm 0.01 (0.97)	-0.09 \pm 0.54	0.279
	CI	0.72 \pm 0.04 (0.72)	0.65 \pm 0.04 (0.65)	-8.70 \pm 4.78	1.68e-07
	CN	0.70 \pm 0.04 (0.70)	0.64 \pm 0.04 (0.64)	-8.79 \pm 4.69	1.68e-07
	CGI	80.09 \pm 2.36 (79.83)	77.23 \pm 2.09 (77.07)	-3.55 \pm 1.61	1.68e-07
II (n=16)	TC	0.98 \pm 0.01 (0.98)	0.98 \pm 0.01 (0.98)	-0.11 \pm 0.46	0.234
	CI	0.73 \pm 0.03 (0.72)	0.70 \pm 0.03 (0.71)	-4.21 \pm 3.38	0.001
	CN	0.72 \pm 0.03 (0.71)	0.69 \pm 0.03 (0.69)	-4.32 \pm 3.38	0.001
	CGI	80.87 \pm 2.35 (81.09)	79.91 \pm 2.16 (79.95)	-1.18 \pm 0.78	6.43e-04
III (n=15)	TC	0.95 \pm 0.07 (0.97)	0.94 \pm 0.08 (0.97)	-0.81 \pm 1.99	0.169
	CI	0.70 \pm 0.10 (0.69)	0.66 \pm 0.10 (0.65)	-6.12 \pm 7.43	0.003
	CN	0.66 \pm 0.07 (0.67)	0.62 \pm 0.07 (0.61)	-6.84 \pm 7.95	0.003
	CGI	81.33 \pm 9.93 (80.45)	78.87 \pm 10.22 (78.69)	-3.05 \pm 3.59	0.002
IV (n=23)	TC	0.98 \pm 0.08 (0.98)	0.97 \pm 0.01 (0.97)	-0.91 \pm 1.19	4.83e-04
	CI	0.66 \pm 0.08 (0.67)	0.59 \pm 0.10 (0.62)	-11.11 \pm 7.15	2.70e-05
	CN	0.64 \pm 0.08 (0.66)	0.57 \pm 0.10 (0.59)	-11.91 \pm 7.30	2.70e-05
	CGI	75.90 \pm 4.99 (77.04)	73.70 \pm 5.75 (75.79)	-2.95 \pm 2.57	3.09e-05

a) Target Coverage

An identical PTV coverage was achieved using the MLC-160 and the m3 for groups I, II and III ($p > 0.05$). For group IV despite that the differences were statistically significant, the improvement ratio is negative and modest being on average less than 1% ($-0.91 \pm 1.19\%$). This means that the MLC-160 would cover the targets just a little bit less, to 97% on average, instead of the 98% level achieved by the m3, for this type of irregular lesions as meningiomas.

b) Conformity

CI and CN indices indicate unequivocal statistically significant differences between m3 and MLC-160 for all groups in terms of dose conformity. Differences were higher for lesions with smaller volume ($\leq 0.5 \text{ cm}^3$, group I) or irregular shaped lesions

(group IV). When using the MLC-160, dose conformity deteriorated, on average, by around 9% for group I, 4% for group II, 6-7% for group III and 11-12% for group IV.

c) Conformity/Gradient Index

Regarding CGI improvement ratios were shown to be negative and of around 3% for groups I, III and IV and just of around 1% for group II, indicating the lower performance of the MLC-160.

6.3.2 | Minimum and Maximum target doses

Minimum and maximum doses to the PTV are shown in Table 6.3.

Table 6.3 – Average values of minimum and maximum doses ($\pm 1\sigma$) to the PTV and corresponding improvement ratios for MLC-160 vs. m3. Median values are shown in parenthesis

Group	D _{PTV} (%)	m3	MLC-160	IR (%)	p-value
I (n=36)	<i>D_{min}</i>	0.98 ± 0.01 (0.98)	0.97 ± 0.01 (0.97)	-0.69 ± 1.10	3.06e-04
	<i>D_{max}</i>	1.04 ± 0.01 (1.04)	1.04 ± 0.01 (1.04)	0.01 ± 0.53	0.694
II (n=16)	<i>D_{min}</i>	0.97 ± 0.01 (0.97)	0.96 ± 0.02 (0.97)	-0.41 ± 1.54	0.315
	<i>D_{max}</i>	1.08 ± 0.02 (1.08)	1.08 ± 0.02 (1.07)	-0.02 ± 0.54	0.275
III (n=15)	<i>D_{min}</i>	0.86 ± 0.14 (0.90)	0.85 ± 0.12 (0.89)	-0.39 ± 11.98	0.489
	<i>D_{max}</i>	1.13 ± 0.08 (1.09)	1.13 ± 0.07 (1.11)	-0.30 ± 2.63	0.946
IV (n=23)	<i>D_{min}</i>	0.92 ± 0.08 (0.94)	0.88 ± 0.08 (0.90)	-3.58 ± 4.43	4.69e-04
	<i>D_{max}</i>	1.12 ± 0.06 (1.09)	1.12 ± 0.07 (1.09)	0.75 ± 3.13	0.153

No statistically significant differences were found between m3 and MLC-160 for all groups, in terms of maximum dose to the PTV. Differences in terms of minimum dose were statistically significant for groups I and IV, with negative improvement ratios, which means that for lesions close to OARs and/or irregularly shaped, the MLC-160 would lead to higher underdosages of the PTV.

6.3.3 | Dose to critical structures

For group III and group IV brainstem sparing was studied. Group III includes 15 clinical cases of brain metastases located near the brainstem. Group IV includes 23 clinical cases of meningiomas. Meningiomas appeared in any brain location, including at close proximity to brainstem, optical nerves or chiasm. For this group, in 14 cases

the lesion was located near the brainstem. In just two cases the chiasm and optic nerves were the considered OARs. Therefore, the brainstem was taken as the more relevant OAR to be reported for groups III and IV.

The dose received by 0.1 cm³ of brainstem (D_{0.1cm³}) the volume of brainstem that received at least 12Gy and the volume of brainstem that received at least the prescription isodose are summarized in Table 6.4.

Table 6.4 – Brainstem sparing average values (±1σ) for both collimators. Median values are shown in parenthesis.

Group	Parameter	m3	MLC-160	p-value
III (n=16)	D _{0.1cm³} (Gy)	12.74 ± 1.55 (12.85)	13.61 ± 1.232 (13.17)	0.015
	V ≥ 12Gy (cm ³)	0.56 ± 1.03 (0.21)	0.71 ± 0.95 (0.46)	0.003
	V ≥ pi (cm ³)	0.37 ± 1.04 (0.01)	0.42 ± 0.98 (0.02)	0.065
IV (n=14)	D _{0.1cm³} (Gy)	12.54 ± 1.93 (13.42)	13.14 ± 1.95 (13.57)	0.008
	V ≥ 12Gy (cm ³)	0.29 ± 0.25 (0.32)	0.53 ± 0.39 (0.50)	9.77e-04
	V ≥ pi (cm ³)	0.08 ± 0.08 (0.07)	0.23 ± 0.20 (0.22)	0.002

Figure 6.4 a) and b) displays D_{0.1cm³} received by brainstem for all clinical cases included in group III and for the clinical cases of group IV where the PTV is located at close proximity to the brainstem (n=14), using the m3 and the MLC-160, respectively.

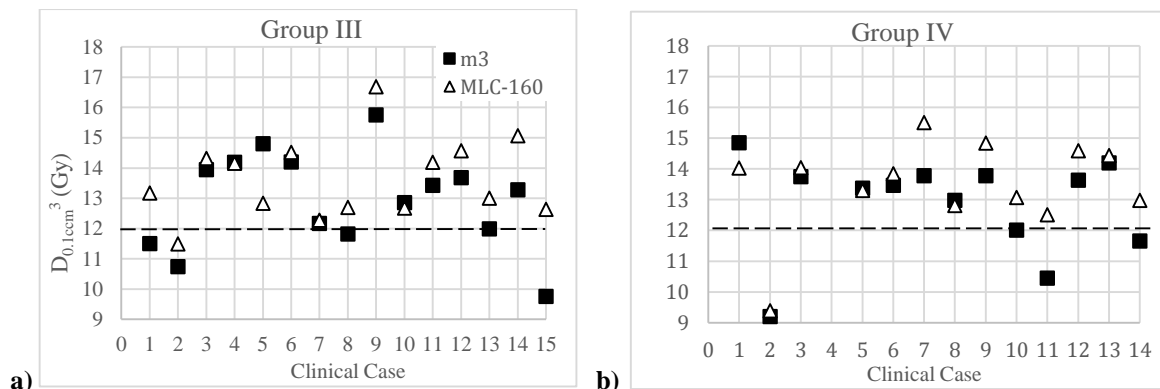


Figure 6.4 – Dose received by 0.1 cm³ of brainstem for a) Group III (metastases close to the brainstem) b) Group IV (meningiomas located close to the brainstem) obtained using the m3 and the MLC-160. The dashed line represents the brainstem tolerance dose, 12 Gy.

A quantitative evidence of improved brainstem sparing for the m3 over the MLC-160 is shown. The MLC-160 contributed on average for an increase in the dose

received by 0.1 cm³ of brainstem of around 1 Gy. When the MLC-160 was used, also the volume of brainstem that received at least its tolerance dose ($V \geq 12\text{Gy}$) is on average, 1.83 times greater than the volume that received the same dose when the m3 was used for group IV. Also for group III this difference is statistically significant but smaller (overdosed brainstem volume 1.27 times greater with MLC-160). The volume of brainstem that received at least the prescribed isodose is on average larger for the MLC-160 in both groups. Although being almost three times greater in group IV, the absolute volume of brainstem receiving at least the prescription dose is reduced, not surpassing 0.23 cm³, on average.

6.3.4 | Dose to normal tissue

The absolute volume of normal brain tissue irradiated to at least the prescribed dose for all lesions is summarized in Table 6.5.

Table 6.5 – Average absolute volume ($\pm 1\sigma$) of normal tissue irradiated to at least 100% of the prescribed dose, V_{NormPI} . Median values are shown in parenthesis. The fourth and fifth columns are respectively the difference in volume for the two MLCs and this volume in percentage to the PTV volume.

Group	m3 (cm ³)	MLC-160 (cm ³)	$\Delta(\text{MLC}_{160} - \text{m3})$ (cm ³)	$\frac{\Delta(\text{MLC}_{160} - \text{m3})}{V_{\text{PTV}}}$ (%)	p-value
I	0.12 ± 0.06 (0.10)	0.16 ± 0.07 (0.12)	0.04	13.24 ± 7.93	1.68e-07
II	1.15 ± 0.83 (0.99)	1.35 ± 0.95 (1.11)	0.20	5.89 ± 4.76	0.001
III	1.53 ± 1.12 (1.54)	1.90 ± 1.57 (1.34)	0.37	9.29 ± 12.28	0.004
IV	2.02 ± 1.72 (1.93)	2.85 ± 2.79 (2.28)	0.83	20.18 ± 16.93	4.01e-05

For all lesion groups there was a statistical significant difference ($p < 0.05$).

According to the types of target, the differences for both MLCs in terms of $V_{\text{Norm100\%}}$ relatively to the V_{PTV} ranged, on average, from around 6% in group II to around 20% in group IV. It is important to evaluate both absolute and relative volumes as, for instance, in group I, the volumetric difference between the two MLCs is just 0.04 cm³ but this small volume represents already more than 13% of the average volume of the metastases in this group. Therefore for group I, III and IV the MLC-160 would lead to higher irradiation of the normal tissue.

6.4 | Discussion

Four groups of clinical cases were created to evaluate the eventual quality loss in treatment plans if the mMLC of BrainLab (3 mm minimum leaf width – m3) presently used for SRS was replaced by an integrated MLC with 5.0 mm leaf width, the Siemens 160 Multileaf Collimator (MLC-160). Plan comparisons included the use of dose-volume data, volumes of normal adjacent tissue and irradiated critical structures, as well as indices to evaluate target coverage and dose conformity.

The plan quality differences mainly result from the different leaf widths and from the impossibility of the MLC-160 leaves to dynamically move along the irradiation arcs according to the beam's eye view. Also other factors such as the leaves transmission and leakage are different in both machines and influence the evaluated dosimetric parameters.

The same planner has done all the plans for the present study and has tried her best to achieve the best possible plan for each clinical case with the two MLC systems, without any time pressure. The average difference between the planning time for the worse cases for the two MLC systems was estimated in around 40 minutes, in favour of m3.

The results demonstrated that identical PTV coverage would be achieved using either the m3 or the MLC-160. Regarding CGIg, dose falloff outside the target was not significantly different for m3 and MLC-160, so the observed statistically significant difference in terms of CGI index was due to a poorer conformity provided by the MLC-160, which is in accordance with what CN and CI indices values revealed.

Concerning the maximum dose received by the PTV, the differences between the two MLC systems were not statistically significant so the dose homogeneity would not change with the introduction of the MLC-160 in the clinical practice. Significant statistical differences were found in terms of the minimum dose to the PTV for groups I (lesions $\leq 0.5 \text{ cm}^3$) and IV (meningiomas). However, the improvement ratio for small metastases ($\leq 0.5 \text{ cm}^3$) was just $-0.69\% \pm 1.10\%$ which may not be clinically significant as for both MLCs the achieved minimum doses were above 95% of the prescribed dose. The minimum dose to the PTV in groups III and IV were always lower than 95% of the prescribed dose which means that close to OARs with lower tolerance doses than the prescribed dose, a compromise is usually established between proper PTV coverage and critical organ sparing trying to reduce toxicity. In these cases, the statistical

significant difference obtained for group IV between the minimum dose to the PTV with the m3 and the MLC-160 may have significant clinical impact. We can preview that the use of the MLC-160 would probably lead to more significant underdosages of irregular lesions close to organs at risk.

Dose conformity was consistently better for the m3 plans than for MLC-160 plans. The effect of target volume was compared for groups I and II. As expected, the dose conformity was higher for larger lesions. Although the conformity of the MLC-160 plans was systematically poorer than that of the m3 plans, both CN and CI indices were, on average, greater than 0.6 which means that the MLC-160 treatment plans would be clinically acceptable as conformal.

Group III included brain metastases located at close proximity or within the brainstem. Therefore organ at risk sparing was a limiting factor that had to be taken into account during planning. Good conformity, with average and median conformity indices above 0.6, could be achieved with both MLCs as was shown in Table 6.2. However the conformity index would assume poorer values in 6-7% if the m3 was replaced by the MLC-160.

The fourth group was formed by meningiomas which are typically irregular lesions. This group had the poorer conformity. With the MLC-160 the plans could not achieve acceptable conformity, on average. The defined improvement ration assumed the highest negative average values (around -12%), meaning that the plan conformity would suffer important decrease with the MLC replacement.

We believe that the higher differences between the two MLC systems in terms of dose conformity for group IV relatively to group III were due to the meningioma irregular shapes. For irregular shape lesions, the static conformal irradiation would represent the highest limitation in the scenario of MLC replacement.

The volume of normal tissue irradiated to at least the prescription dose was consistently greater for plans using the MLC-160 over the m3 for all groups but in higher amount for groups I, III and IV. Table 6.4 shows that the MLC-160 would also contribute for a higher organ at risk affectation. For clinical cases of meningioma or metastases close to organs at risk, therapeutic dose and lesions location could compromise the brainstem tolerance dose, as $D_{0.1\text{cm}^3}$ values showed.

6.5 | Conclusions

If a tertiary 3 mm micro-multileaf collimator of BrainLab presently used for stereotactic radiosurgery was replaced on the Siemens Avant-Garde linear accelerator by an integrated Siemens 160 MLC with 5 mm leaf width, organs at risk sparing and dose conformity of lesions located at close proximity to organs at risk and highly irregular shaped lesions would be the main losses in terms of plan quality. Another important result from the study and still linked with the previously referred ones was that the minimum dose to the PTV would significantly be reduced for the larger width leaf MLC, what would contribute to poorer clinical outcome or higher toxicity as a tradeoff.

The main reason for the observed results was not just the larger leaf width of MLC-160 but the fact that this system integration in the local linear accelerator would have the limitation of not enabling dynamic conformal arcs for the SRS technique.

As a consequence, treatment planning using the MLC-160 has been a cumbersome and time consuming task for all considered groups of lesions, mainly for irregular shaped lesions and lesions located near eloquent areas. The planning time has easily been doubled when compared to the planning time using the m3 collimator which is not an irrelevant issue when real treatment cases are to be considered in SRS where the treatment planning must be done on the same day as the treatment.

Considering all clinical studied cases, 5.56% (2/36) of the cases included in group I, 33% (5/15) in group III and 35% (8/23) in group IV would not be clinically acceptable if the intended replacement of the collimation system would take place. Therefore the eventual MLC replacement would not represent a beneficial option considering the local SRS treatment experience.

6.6 | References

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CHAPTER 7

Conclusions

The objective of speeding up the radiosurgery treatment planning phase was fully accomplished. The first study of this project involved acoustic neurinoma clinical cases and the development of a corresponding specific template. Applying the proposed specific template for acoustic neurinoma, with further adjustment of the mMLC for just two of the six dynamic arcs used for treatment, plan acceptance quality criteria was achieved. This represented a considerable reduction – to around 1/3 – of the treatment planning time.

The acquired know-how about the treatment planning system and associated tools was afterwards applied to major group of SRS clinical cases – brain metastases. Specific templates for different metastatic lesions locations with further adjustment in just three arcs of the 6/7 dynamic arcs used for treatment allow to achieve treatment plans compliance with the local plan acceptability criteria. This contributed for a reduction of the treatment planning time to around 1/2-1/3 without compromising the plan quality. A useful graphical tool was also developed to help the quick choice of the applicable metastase template. This tool and the developed templates are presently used in clinical routine.

The casuistic of all brain metastases treated with linear accelerator based stereotactic radiosurgery was reported and the outcome of SRS was evaluated for 250 metastases in 168 patients treated between March 2008 and December 2014. This study enabled the reporting of the full database of brain metastases treated at IPOCFG. The subsequent statistical study revealed a median overall survival of 9 months from the date of the SRS for a follow-up time of 24 months. Statistical analysis showed that patient's age and primary tumour location were significant predictive factors for survival, whereas the number of brain metastases was not shown to be a significant factor. Local control was achieved in 85.2% of the evaluated brain metastases. No significant factors were associated with the local tumour progression.

Finally, the last study of the project concerned the management decision on dispensing the use of m3 in SRS by replacing it with an integrated multileaf collimator with 5 mm leaf width (MLC-160). The results of the presented work showed that the MLC replacement would imply important drawbacks in terms of plan quality for a significant percentage of the clinical cases treated at IPOCFG. Considering all the studied cases, organs at risk sparing and dose conformity of lesions located at close proximity to organs at risk and highly irregular shaped lesions would be less effective if the intended replacement of the collimation system would take place.

